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SYMPOSIUM ON CANCER OF THE BREAST

Vol. 19 JANUARY, 1946 No. 1

Dr Coller

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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SURGERY

VOL. 19 JANUARY, 1946 No. 1

Original Communications

Symposium on Cancer of the Breast

EXPERIMENTAL INDUCTION OF MAMMARY CANCER*

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THE mammary gland is a frequent site of neoplastic changes not only in man but also in several other species of mammals. It is one of the commoner tumors of the mouse, the dog, and the cat, but is rare in the cow.[19] By far the greatest volume of experimental work on mammary tumors has been performed on mice. Rats and rabbits, at least of special breeds, have been used successfully by some investigators, and more recently work on mammary tumors of dogs has been initiated.

Since most of the developments in this field have not reached the stage of clinical application, they are not generally appreciated, although they have contributed much to the understanding of the cancer problem in general, and of mammary cancer in particular. Especially fruitful have been the studies on the etiologic factors involved in mammary tumors in mice.

INVESTIGATIONS ON MICE

One of the earliest published descriptions of a mouse mammary tumor was made by Crisp in 1854. Scattered descriptions of a few tumors appeared in the literature between 1891 and 1906, in connection with experiments on transplantation of tumors that had their inception and development during that period. Apolant, in 1906, made a noteworthy contribution in his exhaustive and accurate description, classification, and consideration of pathogenesis, based on the study of 276 tumors. Additional studies by Borrel, Michaelis,

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*Sections of this paper dealing with mammary tumors in mice are essentially a condensation of papers in the recent symposium on Mammary Tumors in Mice, written by members of the staff of the National Cancer Institute.[3, 15, 37, 51, 58, 59] References given in that volume are not reduplicated here, and reference is given only to papers that have appeared subsequent to the preparation of the book, or those dealing with species other than the mouse.

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J. A. Murray, Haaland, and others permitted the conclusion that these tumors are malignant epithelial new growths of the mouse, identical in nature with similar tumors of man.

Mammary tumors in mice originate multicentrically from the cells of the mammary epithelium. The tumors may arise from any portion of the mammary tissue, which in the mouse extends over the whole subcutaneous area from behind the ears to the base of the tail except for small midline ventral and dorsal strips. The subcutaneous tumors, readily detected by palpation, grow progressively, and spontaneous regression is rare although by no means unknown.

Microscopically, numerous morphologic variations between different tumors and different areas of the same tumor are encountered. Although in the majority an adenomatous pattern revealing its relation to or derivation from glandular structure is evident, arrangement may be in compact masses, and papillary, cystic, and hemorrhagic areas also are frequent. More rarely, keratinizing, and molluscoid forms may be seen, and a few tumors contain neoplastic connective tissue elements as well, forming carcinosarcomas. Despite these variations, however, the tumors form a pathologic entity, and for most purposes the term "mammary tumor" is adequate. Cytologic investigations of the tumors demonstrate no fundamental changes in the nuclei of the neoplastic cells but reveal interesting variations from the normal pattern of the Golgi material and mitochondria.

Certain changes can usually be recognized in a mammary gland of old mice in which a neoplastic growth develops, and a sudden morphologic change from normal to neoplastic is not found. Cystic dilatation of ducts, chronic inflammatory reactions in the interstitial tissue, and nodular hyperplasia of the mammary epithelium are usual.

The mammary tumors invade and infiltrate contiguous tissue, metastasize to the lungs and other sites, and recur after incomplete removal. The neoplasms can be transplanted into mice of the same genetic constitution, and some grow heterologously in the anterior chamber of the eye of rabbits or guinea pigs.[29] The tumors grow in tissue culture and can be cultivated in the yolk sac of the embryonic chick.[32]

The biochemical constituents of mammary tumors are on the whole very similar to those of other mouse tumors. There is an accumulation of lactic acid, a lower pH, and a higher rate of anaerobic glycolysis than in most normal tissues. The vitamin concentration is near the upper level for other tumors, and the pattern of enzymes is similar to other mouse tumors. The values for the esterase of the blood serum, the catalase activity of the liver and kidney, and the hemoglobin of the blood are lowered with growing mammary, as well as other, tumors.

Soon after the inception of cancer research on mice, it was noted that tumors appeared more often within certain cages of the colonies than within others. The immediate response to the observations of this selective occurrence of tumors was the suggestion of an infectious origin, particularly stressed by Borrel. In opposition to this theory, Loeb's studies suggested that hereditary

factors were involved, and this concept was strengthened by the experiments of several investigators. J. A. Murray's paper of 1911 presented convincing evidence that female mice, in whose immediate ancestry cancer of the breast occurred, were distinctly more liable to develop the disease than mice in whose ancestry tumors were more remote. The experiments of Lathrop and Loeb and of Slye further demonstrated that hereditary factors influenced the formation of tumors. The work, however, encountered a major obstacle because it dealt with heterogeneous stocks. In Slye's case, the lack of homozygous animals and the concept that all tumors could be grouped as a single character contributed to the misinterpretation of the results as indicating a single mendelian recessive inheritance of cancer. As early as 1909, Little foresaw that homozygous strains were essential for an adequate analysis of characters as complicated as tumors. The development of inbred strains of mice, requiring years of accurately recorded inbreeding, was one of the great contributions to cancer research. Experiments with homozygous strains of mice with incidences of mammary tumors ranging from less than 1 to over 90 per cent, developed by Little, Strong, and other geneticists, did not allow postulations of any simple genetic transmission of mammary or other tumors and also showed that different types of tumors are inherited as separate characters. At the same time, the work reiterated that genetic factors were important in the development of such tumors.

It is now established that susceptibility to mammary tumors is not a character with alternative (all-or-none) expression but is expressed in degree. Genetic factors influencing susceptibility are multiple. There is a relationship between mammary tumor development and a known, inherited, single-factor, coat-color trait, lethal yellow (A^y).

The Role of Hormones.—The experimental demonstration of the influence of ovarian hormones on the development of mammary tumors in mice was begun in 1913 by the work of Loeb and his associates. Before these experiments could be started, it was necessary to establish the fact that mammary carcinoma occurred almost exclusively in females, that the incidence of mammary tumors was markedly different in different families or strains kept under similar environmental conditions, and that in each strain the rate of mammary cancer and the average age of the animals at which neoplasms appeared remained fairly stable.

It was found that mammary tumors occurred more frequently in breeding than in nonbreeding mice. In some strains, the incidence of tumors is proportional to the number of pregnancies undergone by the mice. Loeb further demonstrated that the incidence of tumors can be radically reduced by ovariectomy, and that the incidence is related to the age of the animal at the time of ovariectomy. Cori and W. S. Murray substantiated these findings, and the latter succeeded in obtaining mammary tumors in castrated male mice bearing ovarian grafts.

With the advent of chemically isolated estrogens, Lacassagne in 1932 reported the appearance of mammary tumors in male mice injected with these

compounds. The work was rapidly expanded and elaborated by numerous investigators, noteworthy contributions being made by Loeb, Lacassagne, Gardner, Burrows, and Bonser. Most important was the fact that estrogens would elicit mammary tumors in males of strains in which females developed such tumors spontaneously, and in approximately the same incidence. Males of strains in which the tumor incidence was extremely low did not develop mammary cancer no matter how strenuously they were treated with estrogens.

Development of mammary carcinomas in male mice of susceptible strains has been elicited with all the natural and synthetic estrogenic compounds that have been studied from this standpoint. The list includes estrone, estradiol, estriol, equilin, equilenin and their benzoates, diethylstilbestrol and its dipropionate, and triphenylethylene. In general, the carcinogenic activity tended to be related to the amount of estrogen in physiologic units rather than to chemical configuration or other properties. The chemicals could be administered subcutaneously, percutaneously, or orally with the same results, depending on the physiologic activity by the particular route. However, they had to be administered for some length of time, usually about eight weeks or longer, for tumors to appear at a subsequent date. With the compounds in oily or aqueous media, having short periods of activity due to rapid elimination, relatively heavy doses were required to elicit the carcinogenic reaction. When the compounds were given in the form of subcutaneously implanted pellets allowing steady and constant absorption, it was found that the dose of estrogen needed for the induction of mammary tumors was not above that physiologically elaborated by untreated female mice.

These experiments also permitted a thorough microscopic study of the changes in the breast leading to neoplasia.

In the male or the ovariectomized immature female with an intact pituitary, the mammary gland is a rudimentary structure of a few stunted ducts. The ducts begin to proliferate and to dilate within a few days after the administration of estrogens. The ducts soon form buds, and the cells of the proliferating epithelium are large, with clear cytoplasm and vesicular nuclei; an increase in mitoses is detectable by the use of colchicine. In some ducts, the cells become arranged in several layers and secrete an acidophilic product in the form of intracellular and extracellular droplets. The process progresses to the formation of small acinous lobules, so that the rudimentary breast becomes as well developed as that in the normal female. With excessive doses of estrogen, however, the glands become stunted and have localized areas of extensive alveolar development. If administration of estrogen is discontinued at this point, the mammary hyperplasia undergoes gradual regression. With continued estrogenation, there is progressive hyperplasia of the alveoli and ducts; dilation of the ducts, round-cell infiltration, and increase in periductal fibrous tissue are observed inconstantly. In mice of strains in which adenocarcinoma does not develop, the process does not progress beyond this hyperplasia. In mice that develop cancer, there is a multicentric formation of adenomatous nodules which often coalesce, and adenocarcinoma develops in these

centers. Microscopic examination does not reveal any sudden alteration which may be designated as the point at which the normal cells become neoplastic. The site, the growth, and the histologic appearance of mammary tumors elicited in mice injected with estrogens correspond in all details to the description of the spontaneous adenocarcinomas in female mice.

Numerous investigations have been performed in an attempt to discover differences in the morphology or physiology of the breast in mice belonging to strains with different incidences of mammary carcinoma. No clear differences in morphology have been established. In general, however, hyperplasia of the ducts and alveoli under the stimulation of estrogens tends to be more rapid and more uneven, with the eventual development of adenomatous nodules, in the high-mammary-tumor strains. Distention of the ducts into cysts, round-cell infiltration, and an increase in periductal fibrous tissue are inconsistent features apparently not associated with the eventual development of mammary neoplasia.

The morphologic studies also stress that the essential difference between male and female mice, as far as the appearance of mammary carcinoma is concerned, is the practical absence of the mammary gland in the male animals. The formation of the gland and the increase in cellular elements under the stimulation of estrogens thus exteriorize or make possible the development of some factor already present in the animal that leads to the eventual appearance of gross mammary tumors. It is also clear that something more than excess growth is operating in the cancerous transformation of the breast. The onset of recognizable malignant nodules occurs in breeding females or in mice injected previously with estrogens when the major part of the mammary gland is involuting. A difference between the normal growth process and the neoplastic process is also indicated by the unsuccessful attempts to produce a direct transition of the fully developed mammary gland of pregnancy or lactation into a carcinomatous gland by continued injections of large doses of estrogen.

Studies aimed at demonstrating the essential difference between strains of mice that are susceptible to mammary carcinogenesis and those that are not, either spontaneously or under the influence of exogenously supplied estrogens, also took other lines. The estrus cycle of mice of different strains was compared; no correlation was found between the length or regularity of the sexual cycle, duration of keratinization of vaginal mucosa, and the occurrence of tumors. The susceptibility of mice to estrogens, as manifested by the dose required to produce estrus in spayed mice, was not correlated with the susceptibility. The urinary excretion of estrogens and 17-ketosteroids[41] and the ability of the liver to destroy estradiol in vitro do not differ significantly in the low- and the high-mammary-tumor strains. Nor could correlation be established with degenerative changes in the adrenals, the pituitary, or other endocrine organs.

Although the estrogens maintained their focal point in the genesis of mammary tumors in mice, it was shown that other endocrine secretions, especially

those of the adrenal cortex and the anterior pituitary, were involved. Progesterone is reported to reduce the incidence of mammary tumors in susceptible mice.[35] Androgens, given over protracted periods of time, reduce the incidence of such tumors. The action is probably analogous to castration, since androgens suppress the estrus cycle and prevent follicular maturation. The adrenal cortex, in relation to sexual functions, can be considered as a potentially bisexual accessory gland capable of secreting either estrogens or androgens under the influence of stimuli from the pituitary gland. Woolley demonstrated that gonadectomy of young mice of two high-tumor strains led to progressive hyperplasia of the adrenal cortex. There was gradual recovery of the uterus, vagina, and breast from the castrate state, and mammary tumors developed in the females. One male castrated at birth also developed a mammary tumor. In strains that do not develop mammary tumors spontaneously, no mammary tumors were obtained.[65] Mammary carcinogenesis following gonadectomy is probably best explained by the extragenital production of estrogens in the hyperplastic adrenocortical tissue and is dependent upon whether the normal females of the strains under consideration develop tumors of the breast. The origin of estrogens in the adrenals was supported by the close morphologic similarity of the cells of the adrenal nodules to luteinlike cells of the ovary.

The lack of pure anterior pituitary hormones has limited the work on the role of these hormones on mammary carcinogenesis. It has been shown, however, that subcutaneous graft of the hypophysis raises the incidence of mammary tumors in intact females but does not elicit them in males or ovariectomized females. Thus, the pituitary probably stimulates secretion from the ovary; it does not increase the incidence of tumors in strains of mice that do not develop such tumors spontaneously.

It has been indicated that, although various alterations in the hormonal balance of the animal reflect in changed incidence of mammary tumors, the attempts to correlate the degree of genetic or hormonal predisposition to mammary cancer with various physiologic and morphologic manifestations remained unsuccessful. Mice of strains in which the mammary tumor incidence was practically nil did not develop such tumors despite radical estrogenation or other procedures.

The essential difference between mice resistant to mammary carcinogenesis and mice of susceptible strains remained obscure. Much of the clarification was due to investigations in the inheritance of these tumors, which revealed an extrachromosomal factor that was involved.

The Extrachromosomal Factor.—Between 1930 and 1933 the members of the staff of the Roscoe B. Jackson Memorial Laboratory conducted a number of reciprocal hybridization experiments with the high- and low-tumor strains that they had by that time perfected. The results of these experiments, along with these of Korteweg, of Holland, led to the discovery of the extrachromosomal factor in mammary-tumor development and opened the door to one of the most fruitful lines of cancer research of the past decade. The discovery was that the hybrid female offspring resulting from the mating of high-tumor-

strain females to low-tumor-strain males developed tumors in approximately the same incidence as that of the high-tumor strain; but when the reciprocal cross was made, that is, low-tumor-strain females times high-tumor-strain males, the tumor incidence of the female offspring was but little greater than that of the low-tumor strain. Thus, the incidence of the F_1 generation approximated that of the maternal strain.

The Jackson Laboratory group conducted four different experiments including the reciprocal crosses between seven low- and high-tumor strains of mice. The results in all four experiments, entailing a total of 532 F_1 females, were consistent in showing that the tumor incidence of the F_1 females resembled that of the strain of the mother. One cross was carried to the F_2 generation, and it was found that the difference between the reciprocal F_1 hybrids was carried on into the F_2 generation. This generation included a total of 1,139 females, and hence the results were conclusive. However, eight generations of repeated backcrosses of the mice to the low-tumor strain males, thus building up the genetic background of the resistant mice for the extrachromosomol factor, eliminated the extrachromosomal influence and revealed the importance of genetic susceptibility.

Since the genetic constitution even including the sex chromosomes had to be considered the same for the two groups of females resulting from reciprocal crosses between two isogenic lines, it was obvious that this effect was not transmitted through the chromosomes. It had to be some extrachromosomal factor which the female was capable of transmitting to her offspring. It appeared that this factor was likely transmitted by one of three possible routes. It might be transmitted through the cytoplasm of the egg, cytoplasmic inheritance; it might be transmitted through the placenta, an intrauterine influence; or it might be transmitted through the milk, a milk influence.

Bittner undertook the study of the third possibility, the foster nursing problem, and it was through his work that the factor was primarily revealed.

Almost astonishing in its simplicity, the transfer of mice of high-mammary-tumor strains shortly after their birth to foster mothers of low-mammary-tumor strains reduced the occurrence of neoplasms. The low incidence was maintained in subsequent generations; in two strains with a previous incidence of 80 per cent, animals of the tenth to the twentieth generation after a single interruption of the ingestion of milk from their mothers of high-cancer strain had an incidence of less than 2 per cent. When complete interruption of the milk ingestion could be assured, as by removal of the young from the uterus, even a lower residual rate of tumors was encountered. The basic observation has now been repeated and substantiated in one dozen or more independent laboratories throughout the world.

When low-tumor strains of mice are suckled by foster mothers of high-mammary-tumor strains, there is an increase in the incidence of mammary tumors. Whether this increased incidence is maintained or not depends on the genetic susceptibility of the strain. Strain C mice, possessing this genetic susceptibility and having less than 2 per cent incidence of mammary tumors,

were transformed, after nursing on high-mammary-tumor strain foster mothers, into a line having an incidence of over 80 per cent of tumors in the F_2 to the F_{11} generations. In contrast, in mice of strain C57 black, having a high genetic resistance to mammary tumors and the milk agent, the incidence may be increased to as high as 75 per cent by foster nursing them on animals possessing the milk agent,[31] yet in subsequent generations the incidence rapidly decreases as the genetic resistance overcomes the milk influence. Appropriate tests show that these resistant mice lose their ability to transmit or propagate the milk influence to mice of other strains subsequently nursed by them.[3]

It was also established, in at least four independent laboratories, that the induction of mammary tumors in male mice injected with estrogens was also dependent upon whether such animals possessed or did not possess the milk influence. Thus, the agent in the milk is ineffective in the absence of hormonal stimulation of the breast.

Despite the lack of an adequate, rapid bio-assay technique, so that twelve months or longer are required for any particular determination, and despite the lack of stable preparations of the milk agent, depriving the experimentor of a standard sample of reference, much has been learned concerning the nature and properties of the milk agent during the past six years. Most of these contributions have been made by Bittner and his group and by the workers at the National Cancer Institute.

It is known that the agent is present in the milk of high-mammary-tumor strains throughout the period of lactation, although it may vary in concentration during the reproductive period of the mouse. When the young of a high-tumor strain remain with their mothers for varying periods before being foster nursed by resistant-strain females, the young remaining with their mothers for shorter periods develop fewer tumors at a later average age than do the young permitted to nurse from their mothers for longer periods. Other work, in which measured amounts of milk from high-tumor-strain females were fed to susceptible young by means of stomach tube, confirmed this dose-response relationship. A single oral administration of 0.1 c.c. of high-tumor-strain milk to susceptible young mice produced mammary tumors in over 90 per cent of the animals, some eight months later. Evidently there occurs an event in the first few hours of life which leads to the appearance of mammary cancer months later.

The intraperitoneal route of administration of the milk agent is more efficacious than the oral route. In all experiments with the agent, mammary tumors do not appear with any greater frequency at, or near, the site of injection than in other mammary glands of the animals.

The agent is widely distributed throughout the body of the mouse. Tumors have been produced in susceptible mice following subcutaneous implantation of pieces of spleen,[14] lactating mammary gland, and subcutaneous injection of whole blood. The injection of serum of mice has produced a low incidence of mammary tumors whereas a high incidence has been obtained in mice injected with the total cell suspensions of the blood. This fact suggests that the agent is associated with the cellular elements. Extracts of mammary tumors fed to

susceptible mice evoke tumors, a finding demonstrating the presence of the agent in the tumor tissue. Apparently the agent does not penetrate through the placenta. Despite its wide distribution throughout the body, the milk agent is apparently not contagious through body contact.

Adult mice are more resistant to the milk agent than are those up to six weeks of age.[5] There are pronounced differences in degrees of genetic susceptibility of different strains of mice to the milk agent, and the ability of such strains to transmit the agent.[38] Probably the activity of the milk agent differs in some of the strains. The milk influence does not affect the genetic make-up of the mouse in relation to the development of mammary tumors.

Material obtained from lactating mammary tissue of high-tumor-strain mice by filtration through Seitz filters is capable of giving rise to mammary tumors in other mice. Desiccation of lactating mammary gland tissue at room temperature resulted in great loss of activity within one week. Extracts of mammary-tumor tissue to which 50 per cent glycerin was added at 8° C. retained activity for nine days, but were inactive eighty days after the procedure. Lyophilized mammary-tumor tissue suspended in water and fed to mice produced tumors. The preparation was still active when tested six months after lyophilization, although the comparative potency with the original material was not determined, but it was inactive one year following the procedure. The agent survived in mammary tumors p.)pagated in the yolk sac of chicken eggs.[10]

The agent is destroyed in mouse milk heated to 61 or 66° C. for thirty minutes and in fresh mammary tumor extracts heated to 56 or 66° for thirty minutes. It survives in mouse milk kept at 8° C. for fourteen days, is active in extracts of mammary tumors at pH 5.5 to 10.2, but is inactive at pH 4.5. It is not inactivated by acetone or petroleum ether.[8]

Ultracentrifugation experiments showed that the agent when obtained from lactating mammary glands and suspended in distilled water was sedimented at 110,000 times gravity for one hour. Extension of the ultracentrifuge studies revealed that there were two principal components for the active tumor extract, which when extrapolated to zero concentration were 62 S and 90-92 S. However, somewhat similar components were found in the milk of strains of mice with low incidence of spontaneous mammary tumors, as well as in human mammary carcinoma and chick embryo. A minimum molecular weight of three to four million was estimated for the macromolecular material of 62 S, while the faster moving component had a molecular weight of at least five million. The variations of sedimentation rate with concentration indicated an asymmetric particle.

Ultraviolet absorption spectrograms and other tests indicated the presence of a ribose-nucleic acid complex in the material from mammary tumors containing the agent. However, since similar components were present in normal tissues, it is not clear whether the agent inciting mammary tumors in mice is an altered ribose-nucleic acid complex or whether this complex is merely the carrier of the active agent associated with it.

Rabbit serum obtained following injections of saline extract of mammary tumor or with ultracentrifuge pellet material neutralized fresh mouse mammary-tumor extracts in vitro. Intraperitoneal injections of immune rabbit sera protected susceptible mice against the development of mammary tumors following the feeding of active fresh tumor extract.[6]

Filtration and ultracentrifugation experiments show that the milk agent can be transmitted by cell-free material, and its transmission through many generations of mice implies propagation. These features suggest the action of an agent belonging to or related to the viruses.

It is similar to known tumor viruses in its specificity for a certain tissue. It is apparently not involved in the genesis of spontaneous pulmonary or hepatic tumors, of bone tumors,[47, 48] or of induced tumors of the lung, subcutaneous tissues, testes, uterus, or the pituitary.

Unsuccessful attempts to transmit the mouse milk agent to deer mice (*Peromyscus*) suggest that the agent in common with known tumor viruses possesses a degree of specificity; and if a similar factor is active in the occurrence of breast cancer in other species, conclusive tests for its presence must be performed in animals of the same species.

It is not known whether the milk agent continues indefinitely in propagable tumors and whether its presence is required for the continued growth of such transplanted tumors. Preliminary investigations indicate that the presence of the milk agent is not necessary for the propagation of an established tumor, unless a latent phase is postulated.

The mouse mammary-tumor influence differs from known tumor viruses in its relatively long latent period. A mouse ingesting milk shortly after birth will develop a neoplasm six to twenty-four months later. Tumor development is not necessary for transmission of the influence from mother or foster mother to offspring; in fact, under ordinary conditions the causal agent is transferred in the absence of recognized tumor, and this transfer continues for many generations. In this respect, the milk agent acts as a latent virus infection.

Up to the present time, no changes in the organism have been described following the introduction of the milk agent. The mice are not sick and gain in weight equally, as compared with animals without the milk influence. The onset of the estrus cycles and the character of the cycles for the first three months are unaltered. The adrenal changes following estrogen administrations or castration are not influenced by the presence or absence of the milk agent. The agent does not produce consistent and clear-cut alteration of the architecture of the mammary gland.

Other Factors in the Genesis of Mammary Tumors in Mice.—The current concept of the etiology of mammary tumors in mice, as expressed by Bittner, is that at least three factors must be present for their development (1) an inherited susceptibility, (2) hormonal stimulation, and (3) an active agent that is generally transmitted through the milk. All three factors must be present for the genesis of mammary carcinoma. Thus, unless the milk agent is intro-

duced into strains of mice possessing genetic susceptibility (such as strain C), large doses of estrogen do not lead to development of mammary neoplasia. Male mice do not develop tumors of the breast despite the presence of genetic susceptibility or the milk influence unless the lacking hormonal factor is supplied. On the other hand, a quantitative deficiency of any one factor probably can be overcome by the relative quantitative increase in the other two factors. Thus, the relative genetic resistance to mammary tumors in mice of strain C57 black can be overcome by the introduction of the milk factor and sufficient hormonal stimulation.

These three sets of factors, however, by no means exhaust the number of influences that may play a role in the genesis of these tumors. Of these, nutrition has received the greatest attention. Underfeeding of the total balanced diet or of certain essential constituents thereof, such as sulfur-containing amino acids, reduces the occurrence of mammary tumors.

The mere reduction of a balanced ad libitum diet by one-third led to the total suppression of mammary tumors in a highly susceptible strain possessing the milk agent.[40] The mechanism is probably the production of pituitary insufficiency which leads to a lowered level of ovarian secretion and a relative refractoriness of the mammary gland to estrogenic substances. It is known that mice deprived of cysteine in the diet have but few and irregular estrus cycles. It is not known whether diet or other environmental factors influence the transmission and otherwise modify the action of the milk agent, but this does not appear unlikely.

It has been reported that the incidence of mammary tumors is increased and the average tumor age is decreased in mice kept at an environmental temperature of 68° F. as compared with mice living at a temperature of 91° F.[61] Even such mild environmental changes as crowding or isolating animals are reflected in the incidence and time of appearance of mammary tumors, probably because of the effect of these factors on food consumption and the estrus cycle.

Furthermore, data have been accumulating to the effect that not all mammary tumors in mice are associated with or due to the presence of the milk agent. Perhaps the most striking demonstrations have been with animals injected with methylcholanthrene, a polycyclic hydrocarbon that elicits a variety of tumors in mice at the site of introduction (such as subcutaneous sarcoma or cutaneous carcinoma) and at distant sites (such as pulmonary tumors).

In 1939 it was shown that painting of methylcholanthrene on the skin of breeding female mice of a strain that is known to possess the milk agent and genetic susceptibility to mammary tumors (strain dba) accelerated the appearance of mammary tumors. This observation was subsequently repeated in two other laboratories, using the same strain of mice. Mammary tumors were not obtained in male mice, nor was the time of appearance of tumors accelerated in nonbreeding mice. Recently mammary tumors have been elicited by percutaneously administered methylcholanthrene in crosses of two genetically susceptible strains deprived of the milk agent.[42]

Strong and his co-workers reported that a single subcutaneous injection of 1 mg. of methylcholanthrene produced mammary tumors in breeding mice of strains that were characterized by a very low incidence of mammary tumors. Such tumors, usually at the site of injection of the hydrocarbon and often mixed with sarcomatous elements, appeared in 45 of 384 females of the NH strain; of 198 untreated breeding mice, none developed tumors. In a recent summary,[60] it was stated that 75 of 125 breeding females of the NHO strain injected with methylcholanthrene developed mammary tumors, whereas the incidence was 0 in 56 untreated breeding females.

Bonser and Orr in England also reported the appearance of mammary tumors in mice of two strains (IF and CBA) having a very low incidence of tumors in breeding females, following the subcutaneous or intranasal introduction of methylcholanthrene.

The presence of a transmissible agent in the milk of mice of the NH, NHO, and Bonser's CBA strain was excluded by foster-nursing tests. The work suggests that types of stimuli other than the milk agent may produce mammary tumors in mice. The data are not entirely conclusive, however. It is possible that these strains may harbor the agent and not transmit it in the milk. Experiments in which tumor material and other tissues are injected into and fed to susceptible mice deprived of the agent is indicated for further evidence in this problem. The CBA strain is known to be genetically susceptible to mammary tumors; appropriate tests, such as introducing the milk agent into mice of strains NH and IF, have not been reported.

Andervont[4] made crosses between two genetically susceptible strains of mice that were deprived of the milk agent and obtained mammary tumors in 50 per cent of the animals. Moreover, extracts of eleven tumors were fed to susceptible mice and no tumors of the breast were elicited. It was concluded that even these data did not prove the absence of the milk agent in the genesis of the tumors, although they strongly suggested it.

The occasional occurrence of mammary tumors in mice of genetically resistant strains or in susceptible strains that have been deprived of the agent cannot be considered as demonstrating that the milk agent was excluded in the etiology of the tumors. In the first place, if the milk agent is some abnormal and transmissible constituent that arises from the cells or tissues of the animals, rather than an exogenous viruslike infection, its appearance *de novo* by some process like somatic mutation can be postulated. On the other hand, it is difficult to exclude simpler explanations such as accidental transmission of the agent from other mice by means of blood-sucking insects, or by ingestion of tissues or feces of the agent-harboring animals in the same or near-by cages.

Studies on the genesis of mammary tumors of mice indicate that the neoplastic reaction is the end result of an intricate interplay of at least four factors or complexes of factors:

(1) The genetic constitution of the mouse influences mammary tumor development by determining the susceptibility of the mammary tissue to the

hormones and the milk agent, by modifying or altering the mechanism of hormonal stimuli,[13] and by determining the animal's resistance to the milk agent and its transmission. Genetic factors influencing this susceptibility are multiple and are expressed in degree. The ability of the animal to propagate the milk agent and susceptibility to mammary carcinoma may be governed by separate sets of genes.[38]

(2) Hormonal stimuli are essential for the development of the breast and, as such, at least for the creation of a suitable substrate for the action and interaction of other factors that eventuate in the development of mammary tumors. There is no evidence that the hormonal complex has to be abnormal, either qualitatively or quantitatively, for the genesis of mammary tumors in mice. Alterations induced in the hormonal balance by the addition or withdrawal of estrogens and other hormones modify the processes that lead to the development of tumors.

(3) The milk agent, transmitted through the milk of the mother, is necessary for the appearance of most of the mammary tumors in mice. It should be emphasized that the virus nature of this agent is not established. However, if it is a virus, the appearance of mammary tumors would be influenced by variations in the virulence of the agent under various conditions, and its possible latent stages.

(4) Various other environmental factors, such as diet, temperature, and overcrowding, also affect the genesis of mammary tumors, probably by modifying the growth and development of tissues and the hormonal secretions of the animals.

It is probable that at least some of the mammary tumors may require different or additional factors for their appearance and, conversely, that some mammary tumors do not require the presence of the milk agent and are of entirely different etiology. Our knowledge has now reached the stage where we can control most of the factors while varying the one under consideration. This allows a step-by-step evaluation of each of the factors. The shifting of attention from the genetic to the hormonal and thence to the milk influence has been due more to historical developments than to the established relative importance of these different influences. It is clear, however, that there is no single cause of mammary cancer of the mouse, but that the neoplastic reaction is the end result of a complex interplay between many factors.

MAMMARY TUMORS IN OTHER SPECIES

In comparison with the extensive studies on mammary tumors in mice, research on mammary tumors in other species has been fragmentary. Most of the reports are descriptions of more or less incidental findings. Among the few systematic investigations are those of Geschickter, of Wolfe and his coworkers, and of Heiman on rats, and of H. S. N. Greene on rabbits. Even these investigations have been limited to the study of one strain or colony of animals. Much of the work lacks the sound genetic control that has been found essential in, and has characterized the experiments on, mice. The larger size of the

animals, the longer life span, and the lower incidence of tumors, all resulting in greater expense, have been important factors in limiting the advances.

Rats.—The incidence of spontaneous mammary tumors in the rat is low, and the tumors that occur are usually fibroepithelial growths, designated as benign fibroadenomas. Curtis and associates[12] stated that fibroadenomas occurred in 0.9 per cent of the females that survived fourteen months or longer. The incidence for the Rockland colony of rats was 0.8 per cent,[36] and estimates in other colonies were up to 8.0 per cent.[11]

Fibroadenomas of spontaneous origin are transplantable into rats of the same genetic constitution and usually grow progressively to large size.[18] The proportion between the fibrous and the epithelial elements is variable and can be modified by the sex of the host animal or by the administration of hormones. The tumors are more fibrous and grow more slowly in the presence of androgens, and are more epithelial and grow faster in the presence of estrogens.[33, 34, 49, 50] Papillary cysts are encountered occasionally in these tumors. Upon serial transplantation, sarcomatous changes may take place.[36]

Wolfe and his co-workers[11, 63, 64, 66] have studied a colony of rats at Albany (AS strain) characterized by a relatively high incidence of spontaneous mammary tumors. Of 1,827 females surviving for five months or longer, 186 developed tumors at an average age of fifteen months. The animals were not homozygous, and in one line eighteen tumors appeared among eighty females. A study of 149 tumors showed 122 fibroadenomas, 10 fibromas, 11 adenomas, 5 cystadenomas, and 1 carcinoma. The rats of this colony revealed a number of abnormalities which were probably endocrine in character and strongly suggested anterior pituitary deficiency. The estrus cycles were abnormal, fertility was diminished in both males and females, growth was deficient, and prolonged gestation and fetal resorption occurred in a high percentage of the females. Bio-assays of the tumor tissue for estrogen were negative, permitting a supposition that hyperestrinism is not the sole factor in the development of these tumors.

It is not known whether repeated gestations increase the incidence of fibroadenomas in rats. Bagg and Jacksen[7] reported one tumor in a Wistar strain rat that had eleven litters, but no other tumors were encountered in fifty-six breeding females or ten other controls.

Mammary carcinoma of spontaneous origin in the rat is rare, occurring in 0.02 per cent of the females observed by Curtis and co-workers[12] and in 0.05 per cent of the Albany strain. However, mammary carcinoma has been induced consistently with the prolonged administration of estrogens in at least three laboratories.

Geschickter[21-24] used albino rats that had been inbred for seven years. In a colony of over 5,000 animals, no mammary cancer was seen, and less than two per cent developed fibroadenomas at an average age of over eighteen months. Of 555 rats injected with estrogens, 202 developed carcinoma of the breast, although in only 2 cases were metastases present. The author described all stages of development of these tumors from hyperplasia of the ducts and lobules to frank carcinoma. The same morphologic alterations were found in

the breasts of mice under estrogen administrations, with the exception of the pronounced fibrous reaction. In the mouse, increase in periductal fibrous tissue is relatively slight, whereas in the rat the fibrosis is a more striking feature than epithelial proliferation, with formation of fibroadenomas. It is not entirely certain that these estrogen-induced fibroadenomas are identical with the spontaneous tumors, since the induced tumors usually become stationary in size or regress upon cessation of estrogenation[56, 57] and have not been transplanted successfully. The spontaneous tumors usually grow progressively and are transplantable.

The investigations of Geschickter are somewhat confusing because parallels are constantly drawn to human pathology and because an impression may be gathered that the types of lesions obtained can be readily controlled by modifications in the type and amount of the hormone administrations. As in mice, the incidence of mammary cancer is increased and the average tumor age is decreased proportionately with the dose of the estrogen. The estrogens must be given continuously for a period of several months, and slow constant absorption from subcutaneously implanted pellets is more efficacious in eliciting cancer than are intermittent injections of the hormones in oily solutions. The carcinogenic activity of different chemicals with estrogenic activity is related to its physiologic potency and duration of effect rather than to chemical structure or other properties. To produce mammary cancer in the rat, it is apparently necessary to expose the animal to ten or more times the physiologic amount of estrogens. This is probably correct, in contrast with the situation in mice; if only the physiologically elaborated amounts were needed, normal breeding female rats would have a much higher incidence of spontaneous cancer of the breast. Geschickter described eight female rats that developed mammary cancer in twenty-one to sixty days following the implantation of multiple pellets of estrone, estradiol, or diethystilbestrol. This is considerably faster than the earliest appearance of mammary tumors in mice, in which eighty-four days is the shortest recorded latent period. Sex, age, or castration were stated to have little effect on susceptibility to estrogen-induced mammary cancer, although senile animals were more susceptible. The latter point is at variance with similar studies on mice.[45]

Nelson[55] using rats of the Long-Evans hooded strain, in which only 4 fibroadenomas had been seen in fifteen years, reported the induction of 68 carcinomas of the breast in 103 animals. The rats received daily injections of 50 gamma of diethylstilbestrol, or subcutaneously implanted pellets of diethylstilbestrol or estrone. Metastases were present in thirty-three rats. The tumors were classified as: duct carcinoma, thirteen; adenocarcinoma, eight; duct and adenocarcinoma, thirteen; and carcinoma simplex, five. Male and female rats were equally susceptible to the induction of tumors. Eisen[17] obtained two cancers of the breast in fifty-four rats of the Sherman strain implanted with estradiol dipropionate in paraffin.

Dunning and Curtis[16] implanted pellets of diethylstilbestrol in cholesterol into rats of three inbred strains. Mammary cancer developed in 80 per cent

of the animals of one of the strains. Rats of another strain have shown no cancer of the breast after twelve to fourteen months. Reciprocal hybrids between these two strains are being tested for the possible transmission of a milk factor analogous to the milk factor observed in the etiology of mouse mammary tumors.

Wilson and associates[62] reported the induction of mammary tumors in rats with 2-acetylaminofluorene, a nonestrogenic chemical used as an insecticide. The incorporation of the compound in the diet at a concentration of 0.03 per cent or higher for at least ninty-five days led to the appearance of a variety of tumors, especially hepatoma and carcinoma of the urinary bladder, and including three mammary adenocarcinomas in thirty-nine rats. The observation was confirmed by Bielschowsky.[9] Wistar rats were fed 2-acetylaminofluorene, 4 mg. daily for thirty weeks; of thirty-six females, twenty-three developed mammary cancer, and of forty-one males, three developed mammary cancer. It was stated that cancer of the breast could be produced in this strain of rat also by the subcutaneous implantation of diethylstilbestrol pellets.

Rabbits.—Very few cases of spontaneous tumors of the breast of rabbits have been recorded in the literature. Greene[25-28] published a detailed description of a family of rabbits under his observation in which twenty-nine had mammary abnormalities at an average age of 30 months. Eleven rabbits developed frank carcinoma after an average period of 15 months; metastases were found in five cases.

The first indication of mammary disorder in twenty-five animals was a sudden engorgement of all the mammary tissue, so that the glands consisted of large thin-walled cysts. This usually occurred following an infertile mating or estrus period. A slight glandular enlargement in more localized areas sometimes took place unassociated with reproductive activity. The engorgement usually persisted for several weeks and then subsided rather suddenly. Recurrences of the condition finally led to a persistence of small, bluish cysts filled with brown fluid. These cystic areas gradually became firm, and occasionally bloody fluid could be expressed from the nipple. Tumors arose as papillomatous outgrowths from the epithelial lining of dilated acini and duct; these grew continuously, anastamosed with others, and formed acinuslike structures. Invasion of surrounding tissues was next observed, and the cells appeared in adenomatous masses or in solid medullary sheets. The connective tissue response sometimes converted the entire breast into a scirrhous type of growth. Retraction of the nipple, fixation to the skin and muscle, and external ulceration were frequently observed. The duration of life after the appearance of invasion varied from six to forty-eight weeks.

In four rabbits, there was no antecedent mammary engorgement. The tumors appeared as solitary nodules in normal breast tissue and consisted of masses of proliferations of acini. Three of these adenomas progressed within twelve to sixteen months to adenocarcinomas.

Analysis of the factors concerned in the genesis of these tumors showed that the tumors occurred almost exclusively in two family groups of rabbits.

Animals of unrelated lines were foster nursed by tumor-bearing rabbits, but no instance of mammary tumors developed. This is evidence against the presence of a milk-transmissible factor.

Fertility was reduced during the period of mammary disorder in almost all the affected animals; five were completely sterile. The average number of progeny was reduced, and the numbers of resorptions of products of conception and of young born dead in litters were increased.

The pituitary was enlarged in all stages of the disease, but not in rabbits which developed tumors without antecedent mammary abnormality. The pituitary enlargement was due to chromophobe hyperplasia. The endometrium of the uterus was hyperplastic and cystic, and in both groups of rabbits the ovaries frequently contained cysts. The endocrine changes were comparable with those found in animals after long-continued administration of estrogenic substances. It was inferred that the neoplasms represented a natural counterpart of the experimental induction of tumors with estrogens.

Geschickter[23] injected an unstated number of castrated rabbits with daily doses of 0.5 or 1.0 mg. of dimethylstilbestrol. Three rabbits developed papillary cystadenoma of the breast in ten to fifteen months, and in one this progressed to carcinoma at twenty months.

Dogs.—Mammary cancer is one of the commoner forms of canine neoplasia, and the incidence is relatively high in old females.[52, 53] With two exceptions in which dogs with mammary tumors were used for experiments in therapy, publications on this subject have dealt exclusively with morphologic aspects of the neoplasms. Recently, Huggins and Moulder[39] have applied this material to more extensive experimentation.

Most of the neoplasms are mixed tumors containing in addition to neoplastic epithelium, at times, myxomatous tissue, cartilage, osteoid tissue, and bone. The tumors are formed of multiple nodules which may be firm or cystic, and although these nodules are usually well encapsulated and discrete, the skin is sometimes invaded. All breasts may be involved, but the mammary glands of the inguinal region are the most common site. The histologic picture of the epithelium varies in arrangement from small acini to large cysts containing papillary processes. Metastases are found in the regional lymph nodes and in the lungs, usually in the form of papillary carcinomatous cysts. This tissue in transplants to abdominal connective tissue stimulated local bone formation.[39]

Huggins and Moulder studied 120 mammary tumors in 31 dogs. Metastases were present in 4 dogs. All the dogs also had tumors of the adrenal cortex made up of cells which resembled the cells of the zona fasciculata. The adrenal tumors were not confined to females with mammary cancer but were found often in other old dogs, both male and female. The anterior pituitary was usually large in females with tumors.

In nineteen dogs, fluid could be expressed from the nipple overlying a mammary tumor. Solids, fats, calcium, and citric acid were decreased, and the chlorides and alkaline phosphatases were increased in this fluid in comparison with normal milk of dogs. Ovariectomy and adrenalectomy of dogs with tumors did not suppress mammary secretion for prolonged periods.

The importance of the use of the dog in experiments on mammary carcinogenesis needs emphasis because previous studies have been limited to rodents. Inbreeding of dogs in order that homozygous strains may become available has been commenced at the Roscoe B. Jackson Memorial Laboratory.

Guinea Pigs and Monkeys.—There are no reports on the induction of mammary carcinoma in guinea pigs or in monkeys. In reviews of his extensive work on the hormonal induction and suppression of fibroids in guinea pigs, Lipschütz[43, 44] stated that adenofibroma of the breast has rarely been produced but that no carcinomas have been seen.

Three laboratories have injected rhesus monkeys with estrogens for protracted periods without induction of neoplastic changes in the breast. At Yale,[1] in experiments begun in 1930, six monkeys have survived several years' intensive treatment with estrogenic hormones in high doses. Folley and co-workers[20] reported that no carcinomatous changes were observed in the mammary glands of six monkeys which were injected daily with estrone either continuously or for the major part of periods varying between one and three years. Geschickter[23] has maintained six monkeys on continuous injection of estrone or estradiol for over three years without neoplastic effects.

POSSIBLE IMPLICATIONS FOR MAN

It is tempting to speculate how far the experimental findings on animals extend to the genesis of mammary tumors in man. A considerable number of papers drawing such parallels and deductions have appeared in the literature, and reference to man has characterized the publications of a few laboratory investigators. In view of the evident differences in the factors that lead to mammary neoplasia in mice, in rats, and in rabbits, any but the most tentative extrapolations to man must be regarded as unwarranted.

The study of factors that may be of etiologic significance in the occurrence of mammary cancer in man has been based necessarily on statistics. It is well to realize the disadvantages of this approach. The reliability of any data based on histories of cases is always dubious because it extends over such long periods, because of the incipient early symptoms of the disease, and because the attention drawn to the breast in women with tumors of the breast, with its resultant stimulus for remembrance and possible misinterpretations, is absent in the usual control groups of women that may otherwise be carefully selected for comparison. Furthermore, it is too often forgotten that statistical correlation does not imply causal or other direct connection.

There is some evidence that there are significant differences in the incidence of mammary cancer in different populations. This is particularly striking in the low incidence of mammary cancer in Japanese as compared with European women. There is also a predominance of mammary cancer in the ancestry of women with such tumors. Perhaps the most impressive data have been presented by Martynova in Russia, Waaler in Norway, and Wassink in Holland.* Added to the statistically recorded preponderance of mammary can-

*Undesignated references in this section are to be found in the paper by Shimkin.[60]

cer in families of patients with mammary cancer are occasional striking family histories, including simultaneous occurrence of mammary cancer in homologous twins. Whether these cases are coincidences in a relatively common disease, or whether these occurrences have actual significance is not entirely established.

The difficulties encountered in the compilation and evaluation of data on the familial occurrence of mammary cancer in man may be gaged by the extensive work that had to be performed before similar findings were made on noninbred mice. It took three generations, all under continual control and observation, to establish that cancerous ancestry increased the incidence of mammary tumors in the mice colony of J. A. Murray. In rats and rabbits, as well as mice, familial occurrence of mammary tumors has been a striking feature. Such familial occurrence, although necessarily involving hereditary susceptibility, may be due to common environmental conditions, habits, or some transmissible agents or factors.

Mammary cancer occurs but rarely in the male of any species. In man, the comparative incidence with females is in the neighborhood of 1 to 96. This may be attributed to the absence of stimulation by ovarian hormones in the males. It implies that the male breast is a rudimentary organ, and cancer of the breast cannot develop when there is practically no breast. The direct relationship, therefore, is between hormones and mammary development and not necessarily between hormones and mammary cancer.[30, 54]

There is no evidence in the literature that proves that even heavy and protracted use of estrogenic substances has been instrumental in producing mammary carcinoma in women. If parallels are to be drawn between experiments on animals and the danger of the compounds in clinical use, it would have to be decided whether man most closely resembles the mouse, in which mammary tumors are elicited with physiologic doses, the rat, in which the carcinogenic dose is apparently considerably above the physiologic limit, or the guinea pig or monkey, in which carcinomas have not been elicited. Nevertheless, the possibility of carcinogenesis with the heavy, protracted use of these agents cannot be neglected, although of even greater importance is the danger of using such preparations for the treatment of breast masses which are clinically diagnosed as benign, thus leading to procrastination in surgical intervention for possible early carcinoma.

Hormonal stimuli are so essentially involved in all phases of development and function of the breast that it is impossible to dissociate them from the process of mammary carcinogenesis. There is no impressive evidence that the hormonal complex has to be abnormal for the genesis of mammary tumors in mice. On the other hand, it is suggestive that mammary tumors in rabbits are often associated with manifestations of hyperestrinism, and adenofibromas of the breast occur in the Albany strain of rats which show signs of hypopituitarism. In all species that develop mammary tumors sufficiently radical alterations induced in the hormonal balance will undoubtedly be reflected in changes in the incidence and time of appearance of the tumors.

A considerable number of statistical and more direct studies have attempted to ascertain whether hormonal abnormalities are associated with the oc-

currence of mammary cancer in man. No significant differences have been encountered in the histories of the menstrual periods of women with breast cancer as compared with normal women, and investigations of the menstrual cycles of younger women with mammary cancer have yielded no striking observations. Cytologic studies of the pituitary gland of women with mammary cancer showed no deviation from normal. In these respects, the data are similar to the observations on mice.

It has been noted repeatedly that cancer of the breast is more common in the unmarried and nulliparous women than in women who have borne children. Dorn indicated that the incidence is highest in married women without children and concluded that many of these women may be involuntarily sterile. The impression that low fertility in women is associated with a higher incidence of mammary carcinoma is further substantiated by a smaller average number of pregnancies and viable children and a higher percentage of miscarriages in women who develop breast cancer. In this regard, the data on man recall the observations on the Albany strain of rats.

The relation of possible hormonal disturbances to mammary cancer in man has been studied more directly by analyses of urinary excretion of hormones and related substances. Most investigators have concluded that the excretion of estrogens and androgens and other steroids is not abnormal in the presence of cancer of the breast. Recent work at the Memorial Hospital in New York, however, suggests changed quantitative relationship of ketosteroid compounds, probably of adrenocortical origin, in the urine of patients with mammary cancer. The frequent occurrence of adrenocortical tumors in dogs with mammary tumors and in castrated mice is brought to mind. There is yet no clinical evidence, however, of any specific endocrine dysfunction as the cause of mammary cancer in man.

The contention that nonlactation is an important factor in the genesis of mammary cancer, particularly stressed by Adair on the basis of statistics on man and by Bagg on the basis of experimental work on mice, is not impressive. It is probably true that mammary cancer is more frequent among women who do not suckle their children than among women who do. This may be evi dence of a previous inflammatory state or a physiologic deficiency, possibly connected with a predisposition to neoplastic growth, rather than of carcinogenic potentialities of retained or inspissated secretions. Certainly in the mouse, nonlactation per se has little if any direct etiologic relationship to carcinogenesis.

Many clinicians and statisticians have stressed the importance of previous disturbances of the breast in the etiology of mammary cancer in man. Lane-Claypon found significant correlation between the presence of mammary cancer and an antecedent history of nonsuppurative mastitis and structural or functional abnormalities; no significant correlation was elicited in the occurrence of suppurative mastitis, cracked nipples, and trouble with the breast in connection with menstruation. Perhaps as an index of the low reliability of such data, the highest correlation in this series was obtained between external trauma to the breast and subsequent development of cancer in that breast.

An impressive number of authors have subscribed to and developed the view that cystic disease and other benign masses of the breast in women increases the calculated risk of developing carcinoma. From the standpoint of experimental work on animals, this is fully corroborated. In mice, rats, and most of the rabbits, no sharp delineation can be made histologically between normal physiologic hyperplasia, various cystic, adenomatous and papillary abnormalities, and frank malignant growth. In mice the tumors arise as small, compact, adenomatous nodules which progress gradually and continuously into invasive, metastasizing neoplasms; cystic dilatation of the ducts or lobules is of inconstant relationship to neoplasia. In most rabbits, the carcinomas arise as papillary growths in mammary cysts, so that cystic disease is a direct precursor of neoplasia. Whether these processes are continuous, that is, represent different stages of one reaction, or whether some of them represent terminal and separate end results is of course unknown, and decision cannot be made on histologic grounds.

Comparable with the morphologic observations, studies on the physiologic function show a gradual transition from the normal breast to the frankly neoplastic. Hormones, particularly the estrogens, are essential for the development, preservation, and normal function of the epithelium of the normal mammary gland. Tumors of the mammary gland are also dependent upon hormones at least to the extent that the normal tissue from which the tumors must arise is under the control of the hormones. Chronic cystic mastitis and fibroadenoma in women are apparently connected with or depend upon existent ovarian function, although, as Taylor stated, analysis of clinical histories, as well as the estimation of estrogen and prolan in the urine, has not to the present time proved that these conditions are due to any simple excess or lack of estrogenic or gonadotrophic hormone. However, both chronic cystic mastitis and fibroadenoma respond to hormonal stimuli incident to pregnancy and to menopause. Fibroadenoma of the rat is also markedly influenced by hormones. With fully established carcinoma, only a moderate reaction to hormonal stimuli is occasionally noted in some cases. The breaking away of the epithelium from normal hormonal control may be stated as one of the manifestations of the gradually acquired autonomy of the cells.

It is abundantly clear that in all species, carcinoma of the mammary gland is the end result of an intricate, prolonged interaction and combination of at least several factors or complexes of factors. In all species, a degree of genetic susceptibility and a degree of hormonal stimulation are essential, and the process can be modified by numerous secondary influences of internal and external environment. In mice a most important contribution has been made by the discovery of the transmissible milk factor which is necessary before the alteration can proceed beyond the stage of cystic or other hyperplasia. It is not known whether a similar factor is operative in rats, rabbits, or other species. In fact, data are accumulating that suggest it is not essential for the development of all mammary cancers of even the mouse, although the findings by no means eliminate the possibility if latent forms of the agent are postulated.

It is quite possible that similar agents, perhaps in closer symbiosis with the cells and not transmissible in the milk but by intrauterine routes or by the cytoplasm of the ovum, play a similar role in the genesis of mammary carcinoma of other species, including man. It is also evident that, at this time, these are mere postulations, although premature deductions are already appearing in the literature.

Although it is possible that the fundamental mechanism of transformation of normal cells to malignant neoplasms (the so-called intrinsic or formal genesis of cancer) is the same for all types of cells and all species of animals, the inciting factors leading up to the development of the malignant state (the so-called extrinsic or causal genesis of cancer) are obviously different for different types of neoplasia and different species of animals. In fact, it is just as possible that not all mammary carcinomas in one species of animal can be grouped etiologically. For example, it is not established that the mammary cancers of mice in which the milk agent is operative are the same as those induced by the administration of methylcholanthrene, or that the cancers of rabbits which develop on the basis of recurrent cystic disease are the same as those that arise as discrete adenomatous nodules in otherwise normal breasts.

Extrapolation from one species to another and from one type of tumor to another is not warranted at this incipient stage of knowledge of the nature of the neoplastic reaction. It is sounder, at least for the pragmatic purpose of encouraging further progress that must be derived from actual experimentation rather than theorization, to accentuate the careful, patient analysis of each possibly divergent type of cancer, with the well-founded hope that eventually this information may be synthesized into a coherent whole.

REFERENCES

1. Allan, E.: In Report of Activities in 1943. Philadelphia, 1944. The International Cancer Research Foundation, p. 20.
2. Andervont, H. B.: The Milk Influence in the Genesis of Mammary Tumors, in A Symposium on Mammary Tumors in Mice, by members of the staff of the National Cancer Institute, Am. A. Advancement Sc. Publ. 22: 123-139, 1945.
3. Andervont, H. B.: Fate of the C3H Milk Influence in Mice of Strains C and C57 Black, J. Nat. Cancer Inst. 5: 383-390, 1945.
4. Andervont, H. B.: Relation of Milk Influence to Mammary Tumors of Hybrid Mice, J. Nat. Cancer Inst. 5: 391-395, 1945.
5. Andervont, H. B.: Susceptibility of Young and of Adult Mice to the Mammary-Tumor Agent, J. Nat. Cancer Inst. 5: 397-401, 1945.
6. Andervont, H. B., and Bryan, W. R.: Properties of the Mouse Mammary-Tumor Agent, J. Nat. Cancer Inst. 5: 143-149, 1944.
7. Bagg, H. J., and Jacksen, J.: The Value of a "Functional Test" in Selecting Material for a Genetic Study of Mammary Tumors in Mice and Rats, Am. J. Cancer 30: 539-548, 1937.
8. Barnum, C. P., Ball, Z. B., Bittner, J. J., and Visscher, M. B.: The Milk Agent in Spontaneous Mammary Carcinoma, Science 100: 575-576, 1944.
9. Bielschowsky, F.: Distant Tumours Produced by 2-amino- and 2-acetyl-amino-fluorene, Brit. J. Exper. Path. 25: 1-4, 1944.
10. Bittner, J. J., Evans, C. A., and Green, R. G.: Survival of the Mammary Tumor Milk Agent of Mice, Science 101: 95-97, 1945.
11. Bryan, W. R., Klinck, G. H., and Wolfe, J. M.: The Unusual Occurrence of a High Incidence of Spontaneous Mammary Tumors in the Albany Strain of Rats, Am. J. Cancer 33: 370-388, 1938.
12. Curtis, M. R., Bullock, F. D., and Dunning, W. F.: A Statistical Study of the Occurrence of Spontaneous Tumors in a Large Colony of Rats, Am. J. Cancer 15: 67-121, 1931.

13. Deringer, M. K., Heston, W. E., and Andervont, H. B.: Estrus in Virgin Strain C3H (High Tumor) and Virgin Strain A (Low Tumor) Mice and in the Reciprocal (A × C3H) F_1 Hybrids. J. Nat. Cancer Inst. 5: 403-405, 1945.
14. Dmochowski, L.: Transmission of the Mammary Tumor Inciting Factor by Splenic Grafting, Brit. J. Exper. Path. 25: 119-120, 1944.
15. Dunn, T. B.: Morphology and Histogenesis of Mammary Tumors, in A Symposium on Mammary Tumors in Mice, by members of the staff of the National Cancer Institute. Am. A. Advancement Sc. Publ. 22: 13-38, 1945.
16. Dunning, W. F., and Curtis, M. R.: Annual Report of Detroit Institute of Cancer Research, and Personal Communications to National Cancer Institute, 1945.
17. Eisen, M. J.: The Occurrence of Benign and Malignant Mammary Lesions in Rats Treated With Crystalline Estrogen, Cancer Research 2: 632-644, 1942.
18. Emge, L. A., and Murphy, K. M.: The Influence of Long-continued Injections of Estrogen on Mammary Tissue, Am. J. Obst. & Gynec. 36: 750-768, 1938.
19. Feldman, W. H.: Neoplasms of Domesticated Animals, Philadelphia, 1932, W. B. Saunders Company.
20. Folley, S. J., Guthkelch, A. N., and Zuckerman, S.: Mammary Gland of Rhesus Monkey Under Normal and Experimental Conditions, Proc. Roy. Soc. London, s. B. 126: 469-491, 1939.
21. Geschickter, C. F.: Mammary Carcinoma in the Rat With Metastasis Induced by Estrogen, Science 89: 35-37, 1939.
22. Geschickter, C. F.: Estrogenic Mammary Cancer in the Rat, Radiology 33: 439-449, 1939.
23. Geschickter, C. F.: Diseases of the Breast, Philadelphia, 1943, J. B. Lippincott Company.
24. Geschickter, C. F., and Byrnes, E. W.: Factors Influencing the Development and Time of Appearance of Mammary Cancer in the Rat in Response to Estrogen, Arch. Path. 33: 334-356, 1942.
25. Greene, H. S. N.: Familial Mammary Tumors in the Rabbit; Clinical History, J. Exper. Med. 70: 147-158, 1939.
26. Greene, H. S. N.: Familial Mammary Tumors in the Rabbit; Gross and Microscopic Pathology, J. Exper. Med. 70: 159-166, 1939.
27. Greene, H. S. N.: Familial Mammary Tumors in the Rabbit; Factors Concerned in Their Genesis and Development, J. Exper. Med. 70: 167-184, 1939.
28. Greene, H. S. N.: Familial Mammary Tumors in the Rabbit; Evolution of Autonomy in Course of Tumor Development as Indicated by Transplantation Experiments, J. Exper. Med. 71: 305-324, 1940.
29. Greene, H. S. N., and Murphy, E. D.: The Heterologous Transplantation of Mouse and Rat Tumors, Cancer Research 5: 269-282, 1945.
30. Greene, R. R., and Brewer, J. I.: Relation of Sex Hormones to Tumors of the Female Reproductive System, Am. J. Roentgenol. 45: 426-445, 1941.
31. Haagensen, C. D., and Randall, H. T.: Milk-induced Mammary Carcinoma in Mice, Cancer Research 5: 352-355, 1945.
32. Heilman, F. R., and Bittner, J. J.: Observations on Mouse Tumors Cultivated in the Yolk Sac of the Embryonic Chick, Cancer Research 4: 578-582, 1944.
33. Heiman, J.: The Influence of Androgenic Hormones on Transplanted Mammary Tumors in White Rats, Am. J. Cancer 39: 178-184, 1940.
34. Heiman, J.: Comparative Effects of Estrogen, Testosterone, and Progesterone on Benign Mammary Tumors of the Rat, Cancer Research 3: 65-69, 1943.
35. Heiman, J.: The Effect of Progesterone and Testosterone Propionate on the Incidence of Mammary Cancer in Mice, Cancer Research 5: 426-430, 1945.
36. Heiman, J., and Krehbiel, O. F.: The Influence of Hormones on Breast Hyperplasia and Tumor Growths in White Rats, Am. J. Cancer 27: 450-473, 1936.
37. Heston, W. E.: Genetics of Mammary Tumors in Mice, in A Symposium on Mammary Tumors in Mice, by members of the staff of the National Cancer Institute. Am. A. Advancement Sc. Publ. 22: 55-84, 1945.
38. Heston, W. E., Deringer, M. K., and Andervont, H. B.: Gene-Milk Agent Relationship in Mammary-Tumor Development, J. Nat. Cancer Inst. 5: 289-307, 1945.
39. Huggins, C., and Moulder, P. V.: Mammary Tumors of Dogs; Lactation and the Influence of Ovariectomy and Suprarenalectomy Thereon, J. Exper. Med. 80: 441-454, 1944.
40. Huseby, R. A., Ball, Z. B., and Visscher, M. B.: Further Observations on the Influence of Simple Caloric Restriction on Mammary Cancer Incidence and Related Phenomena in C3H Mice, Cancer Research 5: 40-46, 1945.
41. Karnofsky, D. A., Nathanson, I. T., and Aub, J. C.: The Urinary Excretion of Estrogens, 17-Ketosteroids, Creatine and Creatinine in High and Low Mammary Tumor Strains of Mice, Cancer Research 4: 772-778, 1944.

42. Kirschbaum, A., and Bittner, J. J.: Relation of the Milk Influence to the Carcinogenic Induction of Mammary Cancer in Mice, Proc. Soc. Exper. Biol. & Med. **58**: 18-19, 1945.
43. Lipschütz, A.: Induction and Prevention of Abdominal Fibroids by Steroid Hormones, and Their Bearing on Growth and Development, Cold Spring Harbor Symposium on Quantitative Biology **10**: 79-89, 1942.
44. Lipschütz, A.: Comparison of the Condition Under Which Estrogens and Carcinogenic Hydrocarbons Are Tumorigenic, Essays in Biology—in Honor of H. M. Evans, Berkeley, 1943, University of California Press, pp. 297-306.
45. Loeb, L., Suntzeff, V., Burns, E. L., and Schenken, J. R.: Incidence of Mammary Carcinoma in Mice Treated With Estrogen; Effect of the Age at Which the Treatment With Estrogen Begins, Arch. Path. **38**: 52-59, 1944.
46. McEuen, C. S.: Occurrence of Cancer in Rats Treated with Oestrone, Am. J. Cancer **34**: 184-195, 1938.
47. Miller, E. W., and Pybus, F. C.: The Inheritance of Cancer in Mice, With Special Reference to Mammary Carcinoma, Cancer Research **5**: 84-93, 1945.
48. Miller, E. W., and Pybus, F. C.: The Effect of Foster Nursing on the Incidence of Spontaneous Mammary Carcinoma in Two Inbred Strains of Mice, Cancer Research **5**: 94-101, 1945.
49. Mohs, F. E.: The Effect of Estrogens and Androgens on Growth of Mammary Fibroma in Rats, Am. J. Cancer **38**: 212-216, 1940.
50. Mohs, F. E.: The Transformation of Rat Mammary Adenofibroma to Fibroma by Androgens, Cancer Research **1**: 151-153, 1941.
51. Morris, H. P.: Diet and Some Other Environmental Influences in the Genesis and Growth of Mammary Tumors in Mice, in A Symposium on Mammary Tumors in Mice, by members of the staff of the National Cancer Institute, Am. A. Advancement Sc. Publ. **22**: 140-161, 1945.
52. Mulligan, R. M.: Multiple Primary Tumors in Dogs, Cancer Research **4**: 505-509, 1944.
53. Mulligan, R. M.: Some Endocrinologic Considerations of Canine Neoplastic Diseases, Arch. Path. **39**: 162-171, 1945.
54. Nathanson, I. T.: The Relationship of Hormones to Diseases of the Breast, SURGERY **16**: 108-140, 1944.
55. Nelson, W. O.: The Induction of Mammary Carcinoma in the Rat, Yale J. Biol. & Med. **17**: 217-228, 1944.
56. Noble, R. L., and Collip, J. B.: Regression of Oestrogen Induced Mammary Tumours in Female Rats Following Removal of the Stimulus, Canad. M. A. J. **44**: 1-5, 1941.
57. Noble, R. L., McEuen, C. S., and Collip, J. B.: Mammary Tumours Produced in Rats by the Action of Oestrone Tablets, Canad. M. A. J. **42**: 413-417, 1940.
58. Shimkin, M. B.: Hormones and Mammary Cancer in Mice, in A Symposium on Mammary Tumors in Mice, by members of the staff of the National Cancer Institute, Am. A. Advancement Sc. Publ. **22**: 85-122, 1945.
59. Shimkin, M. B.: Conclusions—Including Discussion of the Possible Implications for Man, in A Symposium on Mammary Tumors in Mice, by members of the staff of the National Cancer Institute, Am. A. Advancement Sc. Publ. **22**: 209-223, 1945.
60. Strong, L. C.: Carcinoma of Mammary Gland Following Injection of Methyl-Cholanthrene Into Mice of NHO Strain, Proc. Soc. Exper. Biol. & Med. **59**: 217-220, 1945.
61. Wallace, E. W., Wallace H., and Mills, C. A.: Influence of Environmental Temperature Upon the Incidence and Course of Spontaneous Tumors in Spayed C3H Mice, Cancer Research **5**: 47-48, 1945.
62. Wilson, R. H., De Eds, F., and Cox, A. J., Jr.: The Toxicity and Carcinogenic Activity of 2-acetaminofluorine, Cancer Research **1**: 595-608, 1941.
63. Wolfe, J. M., Burack, E., and Wright, A. W.: The Estrous Cycle and Associated Phenomena in a Strain of Rats Characterized by a High Incidence of Mammary Tumors, Together with Observations on the Effects of Advancing Age on These Phenomena, Am. J. Cancer **38**: 383-398, 1940.
64. Wolfe, J. M., Burack, E., and Wright, A. W.: Abnormal Growth in a Strain of Rats Characterized by Low Fertility and a High Incidence of Benign Mammary Tumors, Endocrinology **27**: 883-887, 1940.
65. Woolley, G. W., and Little, C. C.: The Incidence of Adrenal Cortical Carcinoma in Gonadectomized Female Mice of the Extreme Dilution Strain, Cancer Research **5**: 193-219, 1945.
66. Wright, A. W., Klinck, G. H., and Wolfe, J. M.: The Pathology and Pathogenesis of Mammary Tumors Occurring Spontaneously in the Albany Strain of Rats, Am. J. Path. **16**: 817-834, 1940.

PARENTAL INFLUENCE ON MAMMARY TUMOR INCIDENCE

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THE degree of knowledge which we possess concerning the role of constitutional factors in the etiology of cancer of the breast differs markedly for mice and for human beings. This is not surprising, for it is mechanically much easier to observe the entire life span of mice not only for one but for many succeeding generations. It is also possible to isolate strains of mice by rigid and close inbreeding in a manner entirely impractical for human beings.

Anyone familiar with both types of material will recognize points of similarity and points of difference between them. He will, therefore, be extremely cautious in exchanging or in extending conclusions based upon data derived from either type of material alone. It will be well to examine some of the points of similarity which one finds in human beings and in mice in order to determine, if possible, the categories of experimental findings that might apply to both.

SIMILARITIES IN THE MAMMARY SYSTEMS OF MICE AND HUMAN BEINGS

Function.—The function of the mammary system in both mice and human beings is the formation of milk for the feeding of the young from parturition until the development of the ability for independent injestion of food.

Cyclic Changes.—The mammary system follows a series of cyclic changes which are closely related to hormonal activity.

Hormonal Homology.—As far as is known, the hormones controlling cyclic changes in the mammary system are the same in mice and in human beings.

Sex-Limited Incidence.—Largely because of different degrees of development of the mammary system in the two sexes, a situation which in turn may have a hormonal basis, the normal, functional male individuals rarely develop mammary cancer.

Relative Age Distribution.—In both mice and human beings the peak of mammary tumor incidence coincides with the period during which the reproductive activity of the female is on the wane. In both cases, also, the relatively few very early cases which occur tend to be more rapidly growing than those of the later age groups.

Most Frequent Tumor Type.—In both cases the most frequent type of malignant tumor of the mammary system originates in the adenomatous elements of the mammary tissue.

POINTS OF DIFFERENCE

The points of difference are not listed in any particular order of real or apparent importance, but may be summarized as follows.

Frequency of Metastasis.—Metastasis of mammary tumors is much more frequent in human beings than in mice. This may be due in part, at least, to the

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absolute size of lymph ducts and to the relative extent of tumor surface in the two forms.

Amount of Dedifferentiation.—Human mammary tumors tend to reach the "carcinoma simplex" degree of dedifferentiation more frequently than those of mice which retain more commonly recognizable adenomatous structure.

Amount of Metaplasia.—Mice more than human beings tend to show, in the tumor mass, areas of columnar squamous epithelial cells. Whether or not this is due to a more primitive type of tissue reaction in the mammary tissue of mice is uncertain.

Relation to Lactation.—Another possible point of difference is in the relative frequency of mammary cancer in virgin or in breeding females. In mice there is no instance on record in which the incidence of mammary tumors is higher in virgin animals than in breeding females of the same strain. Human data, however, seem to indicate different relationships. There seems to be a general and significant excess of cancer of the breast in unmarried women. Admittedly this classification is a social rather than a purely biologic one. The difference is difficult to explain although certain distinctions seem to hold good as follows.

(1) There will be a higher rate of pregnancy and of lactation among married women as a group than among unmarried.

(2) In so far as normal endocrine function is concerned there seems to be a greater chance that a higher proportion of normalcy will exist among married than among unmarried women.

(3) Abnormal endocrine unbalance is, in certain laboratory material, a predisposing factor in the formation of tumors.

(4) It seems reasonable that these facts may have some bearing on the situation, because the retention of female mice as virgins is carried out on a basis which does not recognize abnormal endocrine function nor are animals which are naturally abnormal retained in a stock because they are not successful breeders.

From this brief comparison it will be apparent that the points of similarity in the two types are much more basic in their biologic significance than are the points of difference. This fact should be borne in mind when clinical or experimental research on the etiology of human mammary tumors is being planned.

ETIOLOGY OF MAMMARY TUMORS IN MICE

We may next review briefly the experimental evidence on the various etiologic agents which affect mammary tumor incidence in mice.

A careful and thorough discussion of this problem has been developed by Bittner who distinguished three main avenues of influence as (1) genetic (chromosomal), (2) hormonal, and (3) through the milk. Each of these may be considered as being of importance in its own way. Apparently the most important is the last named. Its existence was demonstrated as follows.

When a "high tumor" strain is crossed with a "low tumor" strain the incidence of mammary tumors in the first hybrid generation animals depends

primarily upon whether the female parent comes from the high tumor or the low tumor strain. As an example of the tumor incidence in such a cross the following figures may be cited from Bittner.

High tumor ♀ × low tumor ♂ = mammary tumor incidence over 90 per cent.
Low tumor ♀ × high tumor ♂ = mammary tumor incidence under 5 per cent.

Inasmuch as the chromosomal complex in the two categories of first generation hybrid females was identical, it is evident that some powerful influence other than chromosomes is active.

The existence of this difference in the two types of hybrids was recorded by the staff of the Jackson Memorial Laboratory in 1933 and by Korteweg in Amsterdam almost simultaneously.

The next step was to locate, if possible, when and how the influence was transmitted from parent to offspring. This was definitely established by Bittner who fostered newborn young of the two types on nursing females of the opposite sort with the following results.

	NURSED BY ♀ FROM HIGH STOCK	NURSED BY ♀ FROM LOW STOCK
Hybrid ♀'s from high ♀ × low ♂	95.0% tumors	1.3% tumors
Hybrid ♀'s from low ♀ × high ♂	88.6% tumors	1.4% tumors

It is, therefore, clear that the process of nursing is able to transfer from the mother to the newborn young some influence that very largely determines the incidence of mammary tumors in later life.

Nursing as such is not the only way to transfer this type of influence, however. Bittner showed a significant increase in mammary tumor incidence when implants of bits of spleen from a high tumor strain were made in young animals of a low tumor type.

Woolley, Law, and Little also produced a similar result by inoculation of whole blood from high tumor strain animals into young, low tumor strain individuals.

All of these experimental procedures had to be carried out when the animals were young. The reason for this appears to be the fact that the degree of growth and type of mammary gland architecture differ in high and low tumor strains. Van Gulik and Korteweg showed a structural difference in the amount and extent of terminal bud formation in the branches of mammary glands and proved that "fostered" animals developed the general type of gland structure which characterized the strain from which the foster mother was selected.

Fekete, in a comparative study of the mammary glands of high and low tumor strains, has shown very interesting and important differences in behavior of the glands in the two types.

During pregnancy, twenty observations on mammary glands of low tumor females showed one structural or functional abnormality. This was acute mastitis in one female. During lactation sixteen observations showed three cases of acute mastitis and one case of obstruction of a nipple. During resting periods eleven observations showed one case of acute mastitis.

Similar periods observed in animals of a high tumor strain gave the following results. In pregnancy, twenty-one observations showed a large number of abnormalities as follows: Persistent growing area, one; thickened walls of ducts, two; chronic mastitis, two; acute mastitis and metaplasia, one; neoplasms, six; persistent secretory activity, two. In lactation, fifteen observations showed three cases of acute mastitis, two chronic mastitis, two neoplasms. During the resting periods, fifteen observations showed acute mastitis in three, areas of persistent secretion or growth in four, chronic mastitis and metaplasia in one, and neoplasms in two.

Persistence of secretion and growth, failure to adjust locally to the general physiologic level of the gland as a whole, characterized the animals of the high tumor strain.

These differences lead us to the second type of influence operative in the incidence of mammary tumors in mice, namely, those which are hormonal in nature.

It will be well to recognize that any classification based on such a term as "hormonal" will probably be broken down and redescribed as our knowledge of the causes of hormonal variation increases. It may be that the level of hormonal activity can be materially affected by some influence transmitted during nursing or during intrauterine development. It may be that chromosomal factors will be found which determine wide differences in degree of hormonal activity. In fact, one such gene affecting the activity of the hypophysis in mice has already been described and analyzed. It produces defective hypophyseal development and results in the animal being a sterile dwarf. There is every reason to believe that minor differences in degree of endocrine activity might also have a genetic basis.

While further data on the origin of hormonal differences are being collected, however, it is interesting to record the results of studies on the various inbred strains of mice that already exist. The incidence of mammary tumors is very clearly affected in at least one inbred strain of mice by the factor of pregnancy. This strain is the A albino strain, long inbred and, therefore, possessing a high degree of genetic uniformity. Breeding females of this strain produce about 88 per cent mammary tumors while those kept as virgins form only about 5 per cent. This condition may be contrasted with a high tumor stock such as C3H where both virgin and breeding females produce more than 90 per cent mammary tumors with no significant difference between the two groups. A condition intermediate between these two strains is found in the dba (dilute brown) stock where there seems to be about 80 per cent mammary tumor formation in the breeding females and 50 per cent in virgin females.

Endocrine influences on mammary tumor development were demonstrated beyond any doubt by the classic experiment of Murray who, by transplanting subcutaneously in castrated male mice of the dba strain an ovary from a sister animal, caused a considerable number of these "feminized" males to develop mammary tumors. These neoplasms were of the same general type as those commonly developed by virgin females of this same strain of mice.

Lacassagne later showed that it was the estrogenic hormone of the ovary that produced the conditions necessary for mammary tumor development in male animals.

Evidence that absence of ovarian hormones decreased the likelihood of mammary tumor formation in mice of this strain has also been recorded by Murray. Whether, and if so to what degree, this relationship exists in human beings is debatable.

A third type of influence is that exerted through orthodox genetic channels, namely, the chromosomes.

Evidence for this influence is somewhat difficult to obtain because the strong effect of the milk influence and the complications which are introduced by variation in hormonal activity tend to mask the less powerful genetic effect. Bittner, however, has clearly shown that the genetic influence exists and that it is more evident in F_1 generation hybrids than in those of F_2 and subsequent hybrid generations. The quantitative relationship between F_1 and F_2 hybrids and between F_1 hybrids and a backcross between such animals and a low tumor strain suggests that the situation may be eventually analyzed.

The relative incidence of mammary tumors in the three generations of a cross reported by him is as follows: F_1, 95 per cent; F_2, 76 per cent; backcross, 53.5 per cent.

If the genetic influence was due to a single Mendelian dominant, the expectation in this material would be: F_1, 100 per cent; F_2, 75 per cent; backcross, 50.0 per cent.

Very clearly the observed results, in so far as they go, are consistent with that interpretation. They should not, however, be considered as conclusive of the point at issue.

HUMAN DATA

The absence of anything resembling a strain of inbred human beings with known mammary tumor incidence at once limits the study to statistical methods. It would, however, be of the greatest importance to conduct such studies and they would not be unduly difficult or complex. Incidence of all types of neoplasms in a sufficiently large population of surgically ovariectomized women would be of distinct value in comparison with that in a similar sized population of the same age and degree of reproductive activity, with no operations. It might well reveal some results that would provide a basis for estimating more exactly the degree of correspondence or difference between the human and the laboratory material.

Similarly, if one reviews the literature on the genetics of cancer in human beings he is struck with two important facts, or, perhaps better, attitudes on the part of investigators. The first of these is the reliance on human pedigree data which is one of the commoner ways of presenting evidence of hereditary tendencies. It will take only a moment's consideration to realize that unless the individuals included in these pedigrees have been directly observed, the evidence which they present is secondary in nature and must involve at least

some of the factor of heresay. No amount of careful analysis of primary data, which in fact are not completely accurate, can provide the degree of accuracy which is lacking.

Since no institution has collected direct observational records on several generations of human beings one cannot use the published data as confirmation or denial of the application of principles which have been demonstrated in laboratory animals.

This does not mean that the imperfect data on human beings are without value. Such data can be and are *suggestive*. In so far as they go they indicate the probability of familial tendencies to develop not only cancer in general, but cancer of the breast in particular.

The second "attitude" is that seen in extensive and comprehensive statistical studies. Here again the presence of cancer and the subsequent classification of the individual as "cancerous" depend upon the cause of death as recorded by many observers. These observers have different degrees of training and of scientific responsibility and reliability. There is no way of determining the relative degree of accuracy of their records. For this reason massed statistical data must also be evaluated as being of limited importance. They also can be suggestive but not conclusive.

The problem of parental influence in the formation of mammary cancer in man is one which can and should be investigated. Its study would involve direct observation and a program of sufficient duration to enable the research worker to contact two generations at least.

It should be possible to obtain records of several hundred or perhaps 1,000 women who have proved adenocarcinomas of the breast and who have had three or four children now adults. By dividing the progeny according to whether or not they were nursed or were only bottle fed, two groups can be set up. If cancer of the breast in human beings follows the same general type of behavior as mammary cancer in mice, the daughters of cancerous women, especially those nursed by their mothers, should show definitely more cancer of the breast than of organs other than the reproductive system. They should also show more cancer of the breast than their brothers show cancer of any one type. These facts, if established, would do a great deal toward indicating the next line of research to be undertaken.

The demonstration of the existence of a "milk influence" in human beings would at once open the way for a new series of experiments on hormones and on the chemical analysis of the milk itself. It should be relatively easy to dispose of this question in one way or the other even before any specialized center for the study of human biology has been established.

SUMMARY

1. The experimental evidence derived from a study of the etiologic factors affecting mammary tumor incidence in mice indicates that there are three main groups of influences:

(a) "Milk" influence transferred during the period of nursing.

(b) Hormonal influences possibly having a genetic basis.

(c) Chromosomal influences possibly affecting the structure and/or the reaction of the mammary tissue and also the rate and amount of endocrine activity.

2. The results are sufficiently important to justify a study of human material to discover to what extent the conclusions based on laboratory animals may properly be extended to human beings.

3. Care should be exercised in recognizing the limitations of present methods of collecting and analyzing human data.

4. With reasonable foresight and moderate resources much could be accomplished over a five- to ten-year period.

REFERENCES

1. Little, C. C.: A Review of Progress in the Study of the Genetics of Spontaneous Tumor Incidence, J. Nat. Cancer Inst. 1: 727-736, 1941.
2. Bittner, J. J.: Relation of Nursing to Extra-chromosomal Theory of Breast Cancer in Mice, Am. J. Cancer 35: 90-97, 1939.
3. Bittner, J. J.: Possible Types of Mammary Gland Tumors in Mice, Cancer Research 2: 755-758, 1942.
4. Bittner, J. J.: Observations on the Inherited Susceptibility to Spontaneous Mammary Cancer in Mice, Cancer Research 4: 159-167, 1944.
5. Bittner, J. J.: The Influence of Transplanted Normal Tissue on Breast Cancer Ratios in Mice, Pub. Health Rep. 54: 1827-1831, 1939.
6. Woolley, G. W., Law, L. W., and Little, C. C.: The Occurrence in Whole Blood of Material Influencing the Incidence of Mammary Carcinoma in Mice, Cancer Research 1: 955-956, 1941.
7. Van Gulik, P. J., and Korteweg, R.: The Anatomy of the Mammary Gland in Mice With Regard to the Degree of Its Disposition for Cancer, Proc. Nederl. Akad. v. Wetenschappen 43: 891-900, 1940.
8. Fekete, E.: A Comparative Morphological Study of the Mammary Gland in a High and a Low Tumor Strain of Mice, Am. J. Path. 14: 537-578, 1938.
9. Murray, W. S.: Ovarian Secretion and Tumor Incidence, Science 66: 600-601, 1927.
10. Lacassagne, A.: Development of Cancer of the Breast in Mice Injected With Folleculin, Compt. rend. Acad. d. sc. 195: 630, 1932.
11. Murray, W. S.: Some Effects of Ovariectomy Upon Breeding Females, Science 75: 646-647, 1932.

THE PROGNOSIS OF BENIGN LESIONS OF THE FEMALE BREAST

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WHILE a large and as yet undetermined number of cancers of the breast appear to arise without antecedent pathologic change, certain benign lesions predispose to the development of mammary malignant tumors. Some of these lesions have been almost universally regarded as precancerous; some controversy has existed as to the significance of others. At least a portion of this uncertainty was based on confusion in terminology of the lesions.

The more important lesions of the breast will be defined for the purpose of clarity, and their relation to cancer considered.

Many lesions of the breast are variable in extent and degree. Moreover, a breast may not present uniform characteristics throughout, and its physiologic lability further complicates the picture. In any attempt to classify such lesions these points must be kept in mind.

HYPERTROPHY

At or following puberty, one or both breasts may enlarge to an excessive degree. The enlargement does not produce symptoms other than those referable to its size. The consistency is essentially that of a normal breast. On section the breast tissue is diffusely fibrotic. When studied microscopically the enlargement is found to be due chiefly to increase in the connective tissue elements, sometimes associated with periductal edema. The fat may also be considerably increased, but enlargement in breasts which show an appreciable amount of fat should be considered as due probably to obesity rather than to hypertrophy. The epithelial elements of the breast take little part in the process, although there is some increase in the ductal elements. Assays of the urine of these patients for estrogenic hormones usually show the estrogens to be within normal limits, although they may be slightly elevated.[1] This condition does not predispose to the development of carcinoma.

ADENOFIBROSIS

The breast in the lesion of adenofibrosis is diffusely fibrotic or finely nodular. In the early stages the breast shows cyclic swelling, more marked premenstrually and lessening with menstruation. Later, the slight to moderate increase in size becomes permanent. Pain, which is the feature of the process that usually brings the patient to the physician, is ordinarily more severe in the premenstrual period and is relieved by menstruation. The swelling and pain may be accompanied by venous engorgement. The parenchyma of the breast is somewhat

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rubbery. In the earlier stages, the increased consistency may be somewhat focal or even give a finely nodular texture but later the regions of firmness tend to coalesce, producing a single solid mass with rather clearly defined edges. On section the breast shows a fairly uniform dull white color and is clearly fibrous in nature. Through the firm, white, somewhat resilient connective tissue will be scattered small gray or gray-pink foci. Microscopic study reveals these to be regions of periductal and periacinar edema, often with lymphocytic infiltration. Later the collagen is fairly dense. Changes in the epithelial elements are not significant and do not constitute an integral part of the process. Study of hormonal output has not revealed definite abnormalities.[2] This condition rarely persists beyond the menopause; it is not known to be precancerous.

Fig. 1.—Focus of chronic mastitis showing slight epithelial hyperplasia.

CHRONIC MASTITIS

The lesion of chronic mastitis is probably basically adenofibrosis with epithelial proliferation of a mild type or abnormal secretory activity of the mammary epithelium superposed. There may be serous discharge from the nipple. Certain of the cases classified by Nathanson[1] as "nonpuerperal secretion" and by Semb[3] as "microcystic fibroadenomatosis" belong in this group. On palpation of a breast of this type, somewhat granular or nodular and at times firm cordlike structures may be felt, often radiating out from the region of the nipple. The nodules are not hard but somewhat elastic. On section the breast tissue is dull white or sometimes shows a faintly brownish tinge and a scattering of small cystic spaces not much more than visible to the naked eye. Inspissated secretion in small amounts may sometimes be squeezed from the sur-

face. This lesion has been described by Cole and Rossiter as "benign parenchymatous hyperplasia."[4]

Microscopically periacinar and periductal connective tissue is increased and is often edematous. Lymphocytic infiltration may occur. This was the justification originally for calling this lesion "mastitis" but the infiltration is probably not inflammatory. Some dilatation of the ducts will be apparent, the lumens often containing secretion and epithelial debris. Ordinarily the epithelium of the ducts and acini is slightly hyperplastic. In extreme cases the proliferated epithelium may practically fill the ducts. At times there may be in the breast foci of closely packed, almost solid masses of ductal and acinal

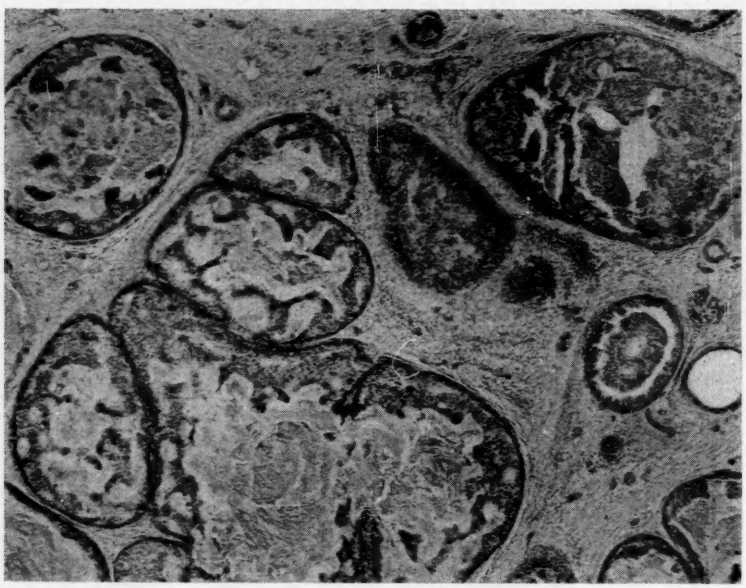

Fig. 2.—Chronic mastitis with marked epithelial hyperplasia and retained secretion.

epithelium, which superficially resemble neoplasia. As was wisely pointed out by Bloodgood,[5] these foci are actually benign in spite of the somewhat bizarre and highly cellular picture that they may present. In its more marked forms, this condition, unlike adenofibrosis, may persist after the menopause. The lesion is probably due to endocrine dysfunction in which the normal cyclic character of the secretion of estrogens has been disturbed. As Nathanson[1] pointed out, the process might be caused by continuous estrogenic stimulation lacking the counterbalance of adequate production of corpus luteum hormone. Somewhat similar changes may be produced in mice by repeated injection of estrogens.[6]

In its milder forms this lesion is not precancerous but in those in which marked epithelial hyperplasia occurs, it must be considered as precancerous. Of special interest in this regard is the use of excessive amounts of estrogenic hormone in women for various purposes. There are instances in which the prolonged use of large doses of estrogens has apparently stimulated proliferation of mammary epithelium with the ultimate development of carcinoma, although such

occurrence has not been proved beyond question. Of interest are the experiments of Lacassagne.[7] Male mice practically never showed breast carcinoma, even in strains of mice selectively bred for a high incidence of mammary carcinoma in females. The prolonged administration of estrogenic hormones to the males produced considerable development of mammary tissue, and in this hyperplastic breast tissue developed a proportion of mammary carcinomas comparable to that in the females.

CHRONIC CYSTIC MASTITIS

Chronic cystic mastitis presents a variety of forms. The one common factor is the development of cysts readily visible, single or multiple. As has been pointed out by a number of observers, these cysts may have entirely lost their epithelial lining, they may be lined with essentially normal epithelium, or they may be lined with epithelium showing varying degrees of hyperplasia and intracystic papillary proliferation. The blue-domed cyst described by Bloodgood usually does not show epithelial hyperplasia in its lining and is then in itself harmless. However, it may be only one feature of a chronic cystic mastitis in which there may be a considerable amount of epithelial activity. When a solitary cyst occurs, this usually is the result of occlusion of a portion of a single duct. Chronic cystic mastitis is most common toward the end of the childbearing period or just after the menopause. As Nathanson[1] pointed out, conditions such as adenofibrosis or chronic mastitis may precede the development of chronic cystic mastitis. Pain is usually absent. Cyclic swelling is not an integral part of the process. A lumpiness of the breast, either localized or generalized, is the chief clinically distinguishing feature. It cannot be too clearly emphasized that given an isolated nodule in the breast, it is impossible to distinguish by physical examination between localized cystic disease and early carcinoma. The nature of such a lesion should be determined by biopsy. After removal of a breast with chronic cystic mastitis, section may show one or more thin-walled bluish cysts varying from several centimeters to a few millimeters in diameter in some portions of the breast tissue and, sometimes elsewhere, masses of inspissated material in dilated ducts or acini or, still elsewhere, grayish, opaque pultaceous or granular circumscribed foci from which, on pressure, a gray or yellowish material may be expressed. The presence of a typical blue-domed cyst is no guarantee that the remainder of the breast tissue is normal and free from malignancy. More than once it has been my experience in sectioning a breast to find present a carcinoma that had not been palpated by the surgeon entirely aside from the cyst which had led to the operation.

Nathanson[1] found no consistent pattern of excretion of estrogens in patients with cystic disease. However, the administration of estrogens with or without prolactin will lead to the production of cystic disease in the experimental animal.

As has already been said, on microscopic observation there may be found a single flattened layer of epithelium lining the cyst or this may have atrophied and left present fibrous tissue alone. There is every gradation from this atrophic lining through several layers of polyhedral epithelial cells to the active proliferation filling the duct with evidence of cellular anaplasia and mitotic activity, which lacks

only the occurrence of stromal invasion to warrant the diagnosis of carcinoma. As Cheatle and Cutler[8] pointed out, "the carcinoma process in the breast begins in an epithelial neoplasia in ducts and acini which continues to grow there before and after there has been a transgression of normal boundaries. . . ." Since by external examination there is no sure way of distinguishing between those forms of chronic cystic mastitis which show little or no epithelial activity and those

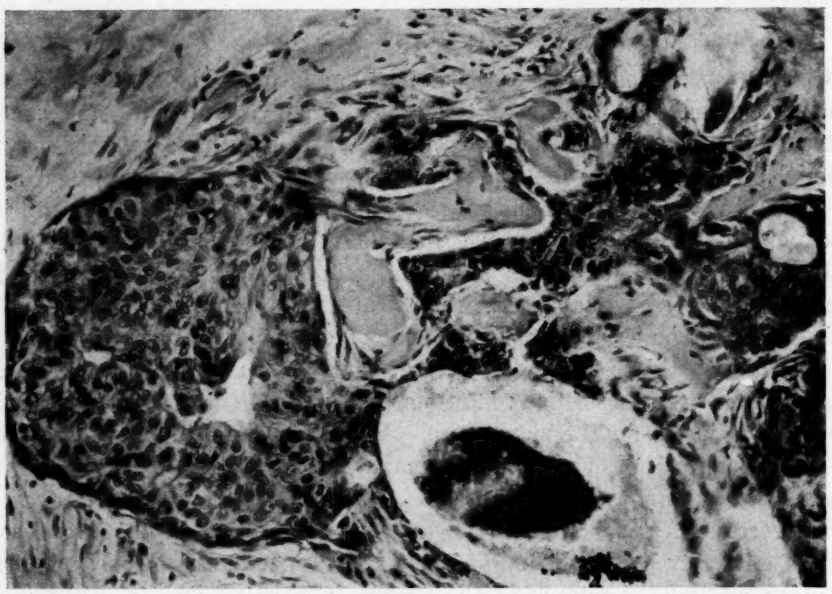

Fig. 3.—Chronic cystic mastitis with intraductal hyperplasia precancerous.

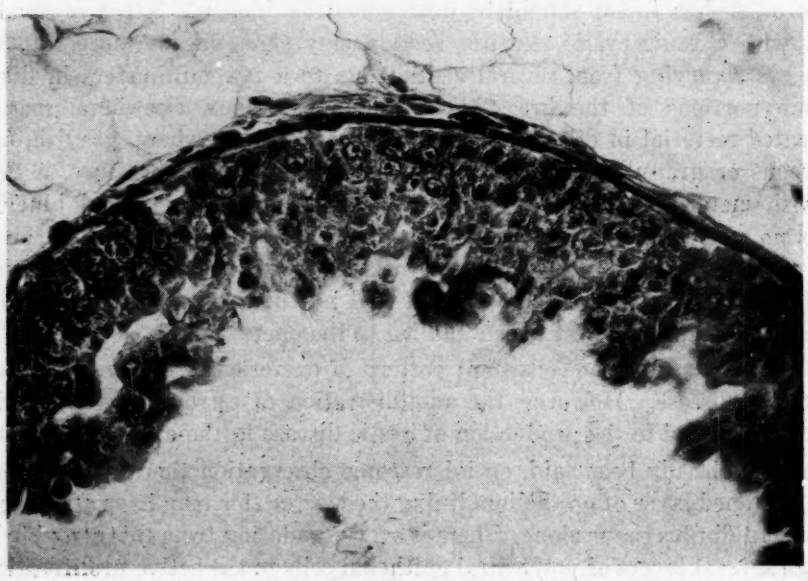

Fig. 4.—Hyperplastic epithelium in chronic cystic mastitis.

which show marked epithelial hyperplasia, the disease must be considered as precancerous.

The follow-up studies carried on in this laboratory several years ago[9] were based on those women who had developed chronic cystic mastitis and the remainder of whose breast tissue had been allowed to remain in place after excision of the local lesion in the breast. Since the worst foci of mastitis were removed, and apparently normal breast tissue left behind, these women should have been partially protected from the development of cancer. However, it was found that in the age group from 30 to 49 years, patients with chronic mastitis and chronic cystic mastitis showed 11.7 times as much carcinoma of the breast as the Massachusetts female population of comparable age. In the women over 50 years of age, 2.5 times as much breast cancer developed. Averaging the entire group, 4.5 times as much breast carcinoma occurred in the group with chronic mastitis and chronic cystic mastitis as in the normal population. On the basis of this and other studies, we can therefore establish the following general rule for the management of chronic cystic mastitis, which must be considered as a precancerous lesion.

If chronic cystic mastitis be localized and the woman be under 50 years of age or be particularly desirous of keeping the breast, no further therapy beyond the removal of the palpable mass is immediately indicated. Such a patient should be followed at semiannual intervals and if a further mass develops, either a simple mastectomy or a radical mastectomy should be done according as the mass is determined to be benign or malignant. Since the lesions in both chronic mastitis and chronic cystic mastitis are apt to be bilateral, the logical procedure would be to amputate both breasts. There is not sufficient risk of subsequent development of carcinoma, however, to warrant or justify bilateral mastectomy. In this opinion Geschickter concurred.[10]

If, on excision of a focus of chronic cystic mastitis or chronic mastitis, there is found evidence of definite precancerous hyperplasia, a simple mastectomy should be performed on the affected side. As has been emphasized by Cole and Rossiter,[4] it is incumbent on the pathologist to take an adequate number of blocks of breast tissue chosen from grossly suspicious areas to determine whether or not the precancerous hyperplasia exists.

INTRADUCTAL PAPILLOMA

Intraductal papilloma of the breast is essentially a complex papillary mass projecting into the distended lumen of a duct. The papillary mass is made up of complexly branching stromal bands often arranged in a frondlike pattern and usually attached at only one point to the wall of the duct. These stromal bands are coated over with epithelium similar to that lining the duct. The epithelium is usually cuboidal, rarely columnar. The most common site is within 2 cm. below the areola although they may be found elsewhere along the course of the ducts. The attachment of the intraductal papilloma is usually by a single stalk, although there may be several. Since the stroma is quite vascular, oozing may occur from its blood vessels, and either bloodstained or frankly bloody discharge from the nipple may result.

The origin of these papillomas is uncertain. They may occur in breasts otherwise normal or in breasts showing varied types of pathologic change. The most varied picture is seen in chronic cystic mastitis where every gradation will be encountered leading from a mere heaping up of epithelium to a complex papillary pattern producing a mass 1 cm. or more in diameter. Frequently the intraductal papilloma develops without relation to any chronic cystic mastitis although Cheatle and Cutler[8] believed that the majority arise in an antecendent cystiphorous process. The lesion may be multiple as well as single. Geschickter[10] found papillomas to be multiple in 17 per cent of his cases. No portion of the breast tissue is immune. Why this change should be most frequent in the ampulla of the terminal ducts is difficult to determine for if the lesion arises on a hormonal basis, one would expect this portion of the mammary epithelium to be least sensitive to hormonal influence. These tumors are rarely bilateral.

Geschickter[10] recognized four types of papillary lesions: papillary hyperplasia in adenosis, which in his series of 680 papillary lesions of the breast accounted for 212 of the group; papillary invaginations too small to be palpated but which produce bleeding at the nipple, 68 cases; benign intracystic papilloma, 203 cases; and papillary cancer, 197 cases. In an analysis of cases presenting bloody discharge from the nipple, Geschickter found it to be present in 102, of 2,460 malignant cases and in 185 of 2,917 benign cases.

It is not unusual in examining sections of intraductal papillomas to find the epithelial cells to be plump with hyperchromatic nuclei and some mitotic figures. At times the only way they can be distinguished from a true carcinoma is by their failure to invade the adjacent normal tissue.

Excision of a grossly recognizable intraductal papilloma may leave others still present in the breast tissue. For this reason there is a predisposition to the subsequent development of carcinoma in a breast from which such a lesion has been excised.[9] Geschickter[10] cited fifty-four cases in which treatment was by local excision, in three of which the patients developed mammary carcinoma subsequently. In neither his series nor Warren's[9] was there a sufficient number of cases to permit any statement beyond the one that the occurrence of intraductal papilloma seems to predispose to the development of carcinoma in a breast and that this lesion is more apt to predispose to development of carcinoma than any other encountered in the breast.

FIBROADENOMA

Fibroadenoma is usually a single but sometimes multiple lesion of the breast, sharply circumscribed and freely movable. Usually spherical or ovoid, its contour may be slightly nodular. On exploration, the tumor is easily separated from the breast tissue. When sectioned the tissue is grayish white or faintly pink with small, more translucent, and sometimes slightly raised foci irregularly scattered on the cut surface. These represent the epithelial elements and their immediate supporting tissue. In a frequently occurring form of the tumor, there are extensive projections of the stroma in the ducts resulting in the familiar intracanalicular picture. This on cut section tends to show a velvety appearance or even faintly visible papillary projections. The stroma

of these tumors ranges from myxomatous to dense, even hyalinized or calcified collagen. In the last seventeen years in this laboratory, 454 fibroadenomas have been examined. Of these, six were calcified. Most were known to have been present for many years. In some of the more long-standing tumors, cysts may develop.

There is some evidence that these tumors are more frequent in nulliparous women with underdevelopment of the breasts.[11] The cells of the fibroadenoma respond to hormonal stimuli. There is not yet satisfactory evidence that they arise as a result of hormonal influence in man, although Nathanson[1] feels that these tumors may represent a localized response to a normal hormonal stimulus. Assay of the excretion of estrogens has not yielded information of positive value.

As has been frequently pointed out, fibroadenoma which occurs in a woman near the menopause is somewhat more apt to become sarcomatous than is one developing in a younger woman. In sarcomatous change of a fibroadenoma, the epithelial-lined glands tend to persist although they may disappear after one or more recurrences and the tumor may grow as a pure fibrosarcoma. The adenofibrosarcoma is a rare tumor and sometimes apparently develops without evidence of a pre-existing fibroadenoma. Geschickter[10] found among 201 patients treated by excision of a fibroadenoma and followed for more than five years 3 per cent of malignant tumors of the breast (carcinomas or sarcomas) appearing. Two of the 484 patients in my series are known to have had recurrence in the form of adenofibrosarcoma. The follow-up, however, was only partial.

Fortunately, adenofibrosarcoma is apt to be of low-grade malignancy and rarely metastasizes to regional lymph nodes. While local rather than radical mastectomy may be adequate therapy, the possibility of metastasis to axillary nodes must be kept in mind.

In my experience fibroadenoma of the breast does not predispose to the development of mammary carcinoma.

REFERENCES

1. Nathanson, I. T.: The Relationship of Hormones to Diseases of the Breast, SURGERY 16: 108-140, 1944.
2. Taylor, H. C., Jr.: The Endocrine Aspects of Chronic Mastitis, Surg., Gynec. & Obst. 74: 326-342, 1942.
3. Semb, C.: Pathologico-Anatomical and Clinical Investigations of Fibro-Adenomatosis Cystica Mammae and Its Relation to Other Pathological Conditions in the Mamma, Especially Cancer, Acta chir. Scandinav. (supp. 10) 64: 1-484, 1928.
4. Cole, W. H., and Rossiter, L. J.: Benign Parenchymatous Hyperplasia, Ann. Surg. 119: 573-590, 1944.
5. Bloodgood, J. C.: The Pathology of Chronic Cystic Mastitis of the Female Breast, With Special Consideration of the Blue-Domed Cyst, Arch. Surg. 3: 445-542, 1921.
6. Taylor, H. C., Jr., and Waltman, C. A.: Hyperplasia of the Mammary Gland in the Human Being and in the Mouse, Arch. Surg. 40: 733-820, 1940.
7. Lacassagne, A.: Apparition de cancers de la mamelle chez la souris mâle, soumise à des injections de folliculine, Compt. rend. Acad. d. sc. 195: 630-632, 1932.
8. Cheatle, G. L., and Cutler, M.: Tumours of the Breast, Philadelphia, 1931, J. B. Lippincott Company, p. 161.
9. Warren, S.: The Relation of "Chronic Mastitis" to Carcinoma of the Breast, Surg., Gynec. & Obst. 71: 257-273, 1940.
10. Geschickter, C. F.: Diseases of the Breast, Philadelphia, 1943, J. B. Lippincott Company.
11. Taylor, H. C., Jr.: The Evidence for An Endocrine Factor in the Etiology of Mammary Tumors, Am. J. Cancer 27: 525-541, 1936.

THE BLEEDING NIPPLE

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THE small number of articles in the American literature of the past ten years dealing with bloody discharge from the nipple would suggest a general acceptance of the significance of this symptom and no challenge to the therapeutic measures recommended.

Variously advocated are simple excision, segmental resection, simple and radical amputation, thus allowing very considerable latitude in procedure adopted for those cases in which frank cancer is not demonstrable.

A brief review of the subject and an outline of procedure is offered in the hope that, without sacrifice to the patients' security, more limited operations and fewer simple amputations will become the practice.

REVIEW OF LITERATURE

The significance of a discharge from the nipple, particularly a bloody discharge, has been variously interpreted. Adair, Judd, and Miller and Lewis have found about the same proportion of benign and malignant lesions responsible for this symptom. MacNeal and Cheatle regarded bleeding as of grave significance.

On the other hand, Cutler and Floyd and Haggard thought that in the majority of cases bleeding was due to small benign duct papillomas and rarely to malignancy. Hart, considering only papillary cystadenoma, found that 48 per cent of the benign, and 12 per cent of the malignant, cases showed discharge as the most prominent symptom. Joel has never seen malignant degeneration in his cases of bleeding breasts. For twenty-three years, Knoflach and Urban did follow-up studies on thirty patients operated upon for bleeding nipple and ten not operated upon. In none did carcinoma develop. According to Bloodgood and Peck and White bleeding is only a symptom and, occurring without palpable tumor, does not demand treatment. Hellwig, Hart, and Floyd and Haggard contented themselves with local excision unless malignancy was found. Hinchey found cancer as the cause of discharge of all kinds, sanguineous and nonsanguineous, in 36 per cent of his cases. Stowers found malignancy in four of ten patients having bloody discharge from the nipple.

Undoubtedly the difficulty in distinguishing between actively proliferating adenocystic disease and cancer has complicated the problem of determining the true incidence of malignancy in patients with bloody discharge.

Bloodgood has aptly called these "borderline tumors" and has pointed out the extreme rarity in which axillary metastases are found. To the unknown degree that pathologists have diagnosed these borderline lesions as cancer, the percentage of malignancy associated with bleeding has been exaggerated.

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FREQUENCY

Sanguineous discharge from the nipple is not a common symptom. Reported series of cases are small. Hinchey quoted Geschichter that, of 5,118 patients coming to Johns Hopkins Hospital because of a breast complaint 6 per cent had bloody discharge.

In 1934, I reported 233 cases of cystic disease, among which there were 8 patients who had bleeding. Of 543 cancers of the breast upon which a radical amputation was performed at the University Hospital, 18 had bloody discharge.

The 55 cases reported in this article represent the total number of patients admitted to the 450 bed Minnesota General Hospital and to a 150 bed private Minneapolis hospital.

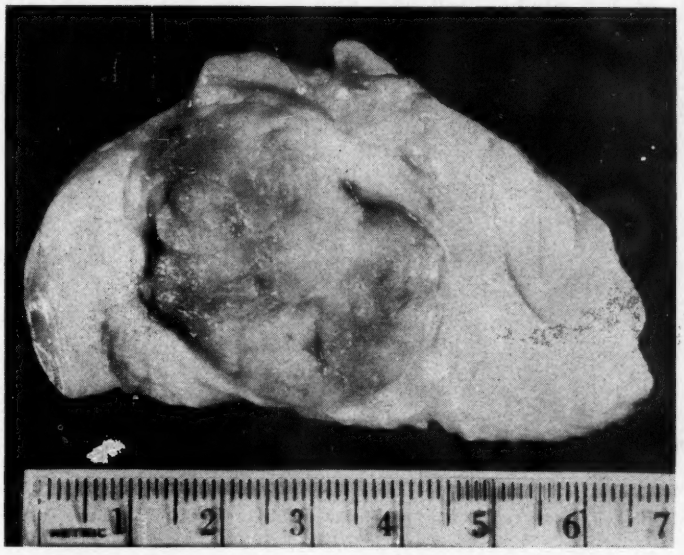

Fig. 1.—A large solitary intraductal papilloma; note the sharp margins of the dilated duct and the papilloma lying free except for the base. The pathologist's interest will be centered in the base and in whether or not there is any epithelial infiltration into surrounding stroma.

ETIOLOGY

The experience of a number of investigators has shown that duct papilloma, carcinoma, and cystic disease are responsible for most of the cases of bloody discharge from the nipple. In the series here reported there were nineteen patients with duct papillomas, twenty-one with carcinomas, thirteen with cystic disease and one with dilated ducts only. In one additional case, exploration was not done, but because discharge has ceased and the case has been followed for nine years, it is assumed that the lesion was benign. The benign lesions totaled thirty-four and malignant lesions twenty-one, approximately 60 per cent benign and 40 per cent malignant.

Other etiologic factors not encountered in this series but reported in the literature are (1) inflammatory lesions, (2) traumatic lesions, (3) hormonal dysfunction, (4) sarcoma, and (5) Paget's disease. Because bleeding is a symptom and not a diagnosis, and because the record rooms did not have a separate

listing for discharge, it is quite likely that a few cases in which surgery was not done have been missed.

DIAGNOSIS

The character of the discharge is merely suggestive. As this discussion is limited to bloody discharge, and since bloody discharge is rightly regarded as of more serious significance than other types, it is well to remember that all types of discharge (with the exception of galactorrhea) need investigation. The outline of procedure which follows may well be applied to patients with non-sanguineous discharge.

Diagnosis is essentially a problem for the pathologist. Frozen sections are not to be relied upon. Because cancers associated with bleeding from the nipple are usually of low malignancy and also because the differentiation between

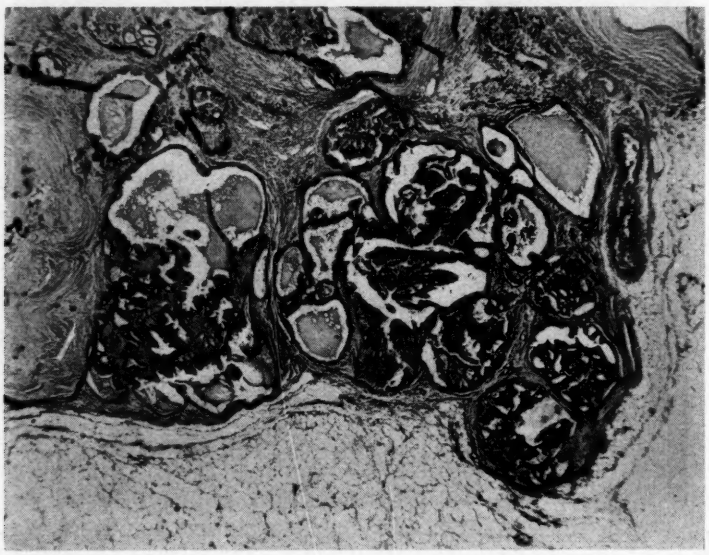

Fig. 2.—Several ducts are filled to varying degrees by papillomas—a good example of diffuse papillomatosis. This lesion commonly occupies a number of ducts and when it is sufficiently disseminated in the breast simple amputation may be required.

cancer and adenocystic disease may be difficult, the surgeon should permit the pathologist time to prepare and study permanent slides.

In the absence of palpable tumor there are three diagnostic aids for the localization of the source of bleeding:

1. Transillumination, as described by Cutler, is easily applied and often definitive if sufficient blood is present to outline a duct, papilloma, or papillomatous cyst.

2. Mammography has been enthusiastically recommended by Hicken and his co-workers. Attempts using this method have been deterred because of severe tissue reactions as reported by Romano and McFetridge and by Sowers and Masson.

3. Pressure tests have proved most useful in our hands. Point pressure by the finger on the various segments of the areola will usually indicate which

TABLE I. SOURCE OF DISCHARGE

Single polyps	(14)	
Diffuse papillomas	(5)	19
Cystic disease		13
Dilated ducts		1
Undetermined (not operated)		1
Total benign lesions		34
Cancer		21
Total patients with bloody discharge		55

duct contains the blood. Often the affected duct, or ducts, stands out a little more distinctly than its neighbors.

TREATMENT

Of the thirty-three nonmalignant lesions twenty-three, or 69.6 per cent, received either local excision or segmental resections, thus permitting the breast to be saved. Of the ten simple amputations, three were done for diffuse papillomata of ducts, two for single papillomas, and five for adenocystic disease sufficiently diffuse to warrant total removal of the breast.

SUGGESTED PROCEDURE

Accepting the dogma that it is better that a woman lose her breast than her life, the determination of the extent of the procedure to be done in any given case is still not easy. To most women the loss of a breast is a tragedy and a definite psychic shock. No one has been able to determine the number of breasts which justifiably may be sacrificed to save a life.

The following outline in general has been the practice and teaching of the department of surgery at the University of Minnesota and bears the approval of the department of pathology.

A. Discharge and Palpable Tumor.—The presence of the tumor alone is sufficient justification for its removal. Local excision may suffice for solitary intraductal papillomas and well-localized adenocystic disease but because the sources of bleeding may be multiple it is better practice to excise the entire duct and its tributary glands. The technique described by Babcock has served well in accomplishing such a limited resection. Only when the pathologist has satisfied himself that the lesion is malignant is radical amputation justified.

B. Discharge and Diffuse Nodularity.—A segmental resection of the duct containing the bloody discharge and its tributary system is done. If cancer is not found and the source of bleeding is eliminated the attitude toward the remaining breast will depend upon the surgeon's attitude toward the role of cystic disease as a potentially precancerous lesion. If he holds the prevalent opinion that the relationship is not close, he will content himself with keeping the patient under observation, always ready to explore any localized area which shows increase in consistency or stands apart from the rest of the breast.

TABLE II. OPERATIVE PROCEDURES

Local excisions or segmental resections (breast preserved)	23
Simple amputations	
Single polyps	2
Diffuse papillomas	3
Diffuse cystic disease	5
Total operations on benign lesions	33

C. Discharge and No Palpable Tumor or Demonstrable Breast Change.—Whenever the source of bleeding can be located the offending duct and tributary glands are excised. Where the discharge is intermittent or scanty it may be difficult to locate the segment of breast or the duct from which the discharge is coming. Under these circumstances it seems entirely reasonable to keep the patient under observation. Repeated examinations will usually permit localization.

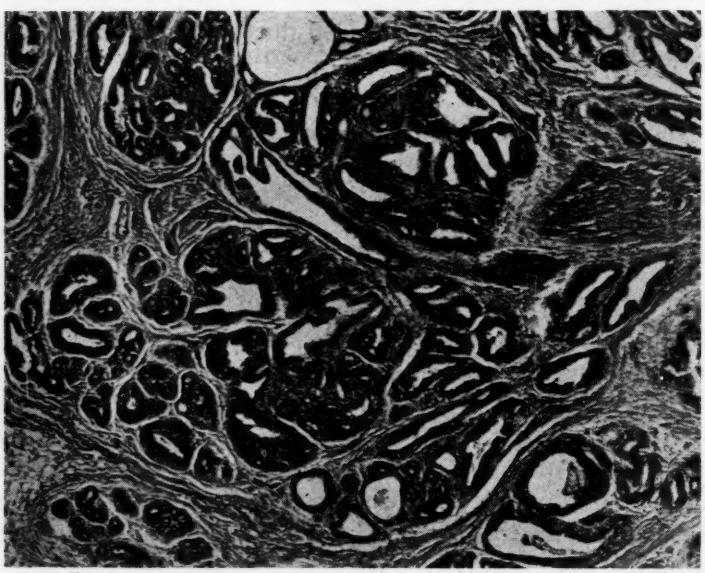

Fig. 3.—An example of a mild form of adenocystic disease which is causing bloody discharge; nothing is seen in microscopic study to indicate why the lesion produces bleeding.

The justification for this policy is based upon the extreme rarity of sanguineous discharge from the nipple caused by cancer and without palpable tumor. Bell stated that in his entire experience as head of the department of pathology at the University of Minnesota there have been no examples of such an occurrence. It is entirely possible among patients showing bloody discharge that an early, small, deeply developing cancer can exist without palpable tumor. Hinchey reported two cases, and Koucky, pathologist to several private hospitals in Minneapolis, has experienced it but once in over 5,000 breast biopsies.

D. Bloody Discharge From Multiple Sources.—A waiting policy is here indicated unless palpation reveals changes in breast consistency which then justifies biopsy of the most suspicious area. Bleeding of such nature may subside spontaneously. I have observed such a case, occurring bilaterally at the end of a period of lactation and subsiding completely within a few months. Papillomas may undergo fibrotic changes, even calcification.

E. Pseudosanguineous Discharge.—A dark green, sometimes grumous discharge from the nipple may easily be mistaken for bloody discharge. When a single duct is the source, excision is warranted for the patient's peace of mind. The excised duct will show ectasia only. There will be little or no sign of

epithelial activity. The dilatation may involve even the smaller tributary ducts in the periphery of the breast. When multiple ducts are involved and no masses except the ducts themselves are palpable, the condition need not be disturbed since sacrifice of the whole breast is unnecessary.

F. Persistent or Nonlocalized Bleeding.—Persistent bleeding from multiple sources or bleeding which cannot be localized may warrant simple amputation. Especially is this true in older women where the loss of the breast is not a tragedy, or where the patient herself may elect to end her state of uncertainty or apprehension. It is difficult to be dogmatic in advising a patient to accept amputation because percentagewise, even with the symptoms listed, she may still carry her greatest total risk from cancer arising in other sites than the breast. If she elects to keep her breast, who can say that she is not justified?

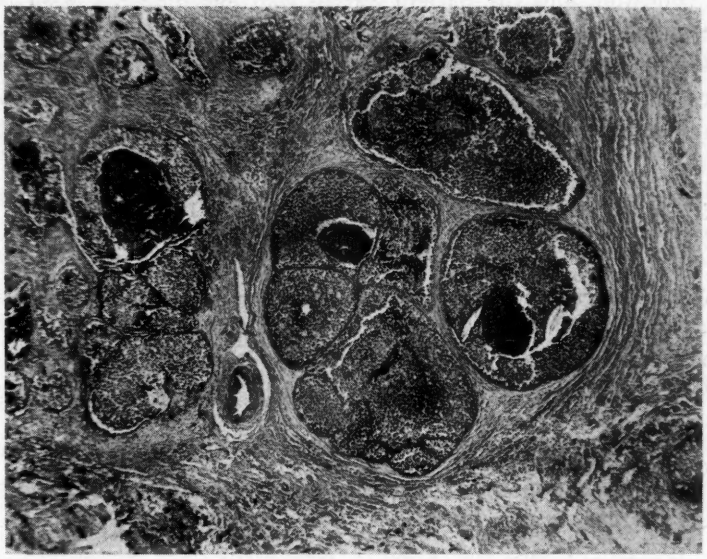

Fig. 4.—Adenocystic disease with marked intraductal epithelial growth; note blood filling the duct spaces. Some pathologists call this carcinoma grade I. Others believe it is benign, but all will insist that the entire lesion be removed from the breast.

SUMMARY AND DISCUSSION

It is my conviction that too much fear, even panic, has been exhibited toward the symptom of bloody discharge from the nipple. It is my conviction that a truly representative report of all cases would reveal a lower percentage of malignancies responsible for the symptom. The inadequacies of the filing systems which do not provide for indexing the symptom of bloody discharge undoubtedly account for the loss of some benign cases from this series, whereas all of the cancers are included. Then, too, it is likely that procrastination or subsidence of symptoms deters a certain number of women from reporting the bleeding, whereas all malignancies eventually drive the patient to seek medical attention.

Bloody discharge can never be overlooked or ignored until cancer has been ruled out. In younger women where the source of the bleeding cannot be localized, where it is intermittent, recurrent, or involves a number of different ducts.

and no palpable tumor exists, the patient's hazard does not merit removal of the breast. Likewise, in younger women when the source of bleeding is revealed to be adenocystic disease, even though the remainder of the breast may harbor more of the disease, it is my opinion that local excision is sufficient. Unless further bleeding develops which requires investigation, the patient should merely be kept under observation as any other patient who manifests adenocystic disease.

Whether the surgeon believes that there is no relationship between cystic disease and cancer, or whether he believes that the incidence of cancer is higher in adenocystic disease, the risk does not justify the removal of breasts in young women. In later life when the period of function is past and the loss of the breast is less of a tragedy the situation may be altered. If the surgeon believes that the patient is exposed to a greater than ordinary risk of cancer because of the breast condition and the patient agrees that she does not wish to undergo the risk, a simple amputation may be done.

In seeking to preserve breasts by the application of these views, I know of no instance where this advice or plan of procedure has resulted in delay or failure to recognize a malignancy.

REFERENCES

Adair, F. E.: Sanguineous Discharge From the Nipple and Its Significance in Relation to Cancer of the Breast, Ann. Surg. **91:** 197, 1930.

Babcock, W. W.: A Simple Operation for the Discharging Nipple, SURGERY 4: 914-916, 1938.

Bell, E. T.: Personal communication.

Bloodgood, J. C.: Benign Lesions of the Female Breast for Which Operation Is Not Indicated, J. A. M. A. **78:** 859, 1922.

Idem: Border Line Breast Tumors, Ann. Surg. **93:** 235, 1931.

Campbell, O. J.: Relationship Between Cystic Disease of the Breast and Carcinoma, Arch. Surg. **28:** 1001-1056, 1934.

Cheatle, G. L.: Clinical Signs and Indications of Changes in the Breast, Practitioner **122:** 69, 1929.

Cutler, M.: Transillumination as an Aid in the Diagnosis of Breast Lesions, Surg., Gynec. & Obst. **48:** 721, 1929.

Idem: The Diagnosis and Treatment of Precancerous Lesions of the Breast, Illinois M. J. **61:** 313, 1932.

Floyd, W. O., and Haggard, W. D.: A Study of Five Hundred Breast Cases With Surgical End Results, J. Tennessee M. A. **23:** 24, 1930.

Hart, D.: Intracystic Papillomatous Tumors of the Breast, Benign and Malignant, Arch. Surg. **14:** 793, 1927.

Hellwig, C. A.: Die chirurgische Indikation bei chronischer cystischer Mastitis, Arch. f. klin. Chir. **159:** 763, 1930.

Hicken, N. F., Best, R. R., Hunt, H. B., and Harris, T. T.: The Roentgen Visualization and Diagnosis of Breast Lesions by Means of Contrast Media, Am. J. Roentgenol. **39:** 321, 1938.

Hinchey, P. R.: Nipple Discharge, Ann. Surg. **113:** 341, 1941.

Joel, W.: Die maladie kystique der Brustdruse, ihre Entstehung und ihre maligne Entartung, Monatschr. f. Geburtsh. u. Gynäk. **85:** 358, 1930.

Judd, E. S.: Intracanalicular Papilloma of the Breast, Journal-Lancet **37:** 141, 1917.

Knoflach, I. G., and Urban, K.: Zur Pathologie und Therapie der "blutenden Mamma," Arch. f. klin. Chir. **150:** 355, 1928.

Koucky, R. W.: Personal communication.

MacNeal, W. J.: Chronic Cystic Mastitis, S. Clin. North America **12:** 523, 1932.

Miller, E. M., and Lewis, D.: Significance of a Sero-Hemorrhagic or Hemorrhagic Discharge From the Nipple, J. A. M. A. **81:** 1651, 1923.

Peck, C. H., and White, W. C.: Tumors of the Breast, Benign and Malignant, Ann. Surg. **75:** 641, 1922.

Romano, S. A., and McFetridge, E. M.: The Limitations and Dangers of Mammography by Contrast Mediums, J. A. M. A. **110:** 1905-1910, 1938.

Sowers, B. F., and Masson, J. C.: Mastitis Following Use of Thorium Dioxide: Report of Case, Proc. Staff Meet., Mayo Clin. **12:** 528-531, 1937.

Stowers, J. E.: The Significance of Bleeding or Discharge From the Nipple, Surg., Gynec. & Obst. **61:** 537-543, 1935.

INTRADUCTAL BIOPSY OF CERTAIN PATHOLOGIC PROCESSES OF THE BREAST

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AS A complement to the roentgen-ray study of the duct system of the breast, and in cases of evident lesions of the milk duct or its main branches seen on the x-ray film, a curettage or biopsy of these processes has been performed endo-ductally. Thus, this has presented one more opportunity for the diagnosis and treatment of mammary diseases.

Intraductal growths that frequently are found near the nipple, and which dilate the ducts as they develop, are the lesions most suitable for this new diagnostic procedure.

In previous articles I have pointed out that when injecting a milk duct, especially if there is a reflux of the liquid, abundant ductal secretions are emitted, and also small tumoral fragments in cases of intraductal growths, which afford a proper histologic examination.

TECHNIQUE

The technique of the intraductal biopsy consists of two steps: first, radiographic localization of the pathologic process, that is, determination of the diseased tubular-acinous gland and localization of the pathologic process in it, and, second, the biopsy. The first part is a purely x-ray technical problem, and it shall only be stated here that as contrast media we employ concentrated iodized solutions used in intravenous urography.

Once the pathologic process which we desire to curette is localized, the biopsy is then done by two stages. First, the slow dilatation of the orifice of the milk duct is accomplished by means of small metal dilators, such as are used in ophthalmology for the dilatation of the lacrimal orifice. Lubrication of the nipple with olive oil facilitates these operations.

In certain cases the dilatation is completed with the use of a small bougie (Laminaria), which must be introduced slightly in order to dilate only the sphincter of the ductal orifice. Care must be taken that it is not introduced too far, as some difficulty may be found in extracting it. In such circumstances a slight local anesthesia proves useful.

Second, after securing sufficient dilatation to permit the introduction of one of our delicate instruments, with a fine curette, wire loop, or small forceps (according to the type of lesion and size of the duct), the biopsy is easily obtained. The pathologist is able to make a satisfactory histologic study from the specimens obtained in this manner.

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Thus, the problem of bleeding from the nipple is partially solved; the x-rays will show whether or not there exists an intraductal neoplastic growth, and they will give us information as to its extension, location, number, and probable etiology, which will often be confirmed by the histologic study of the biopsy obtained endoductally.

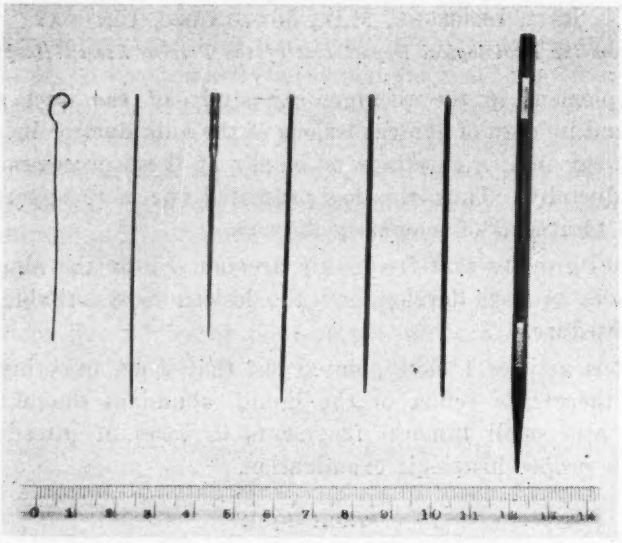

Fig. 1.—Dilators of the milk duct orifice.

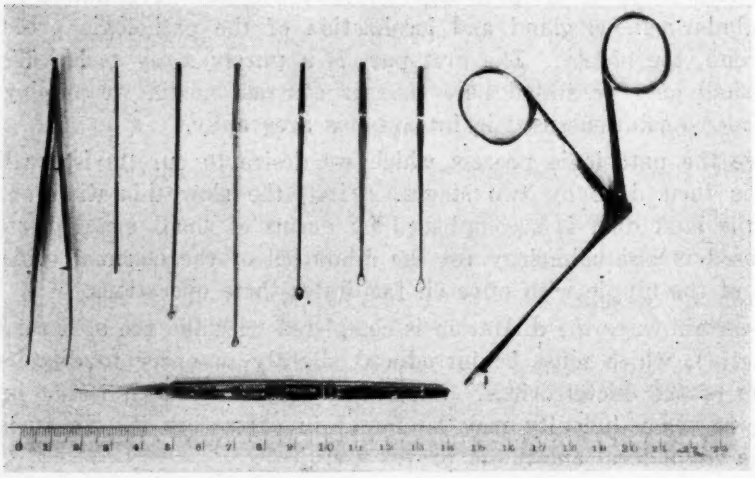

Fig. 2.—Different instruments used for biopsy.

When the biopsy reveals only a benign papillary lesion the possibility must never be absolutely discarded of a malignant transformation in that part of the tumor from which no biopsy was taken, because these lesions must be looked upon as precancerous conditions, and this transformation must always be suspected in large papillary adenomas, notwithstanding a negative biopsy.

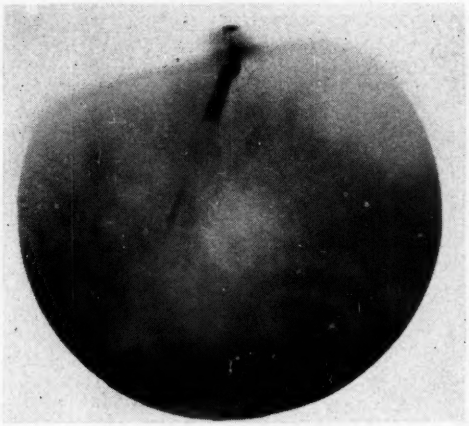

Fig. 3.

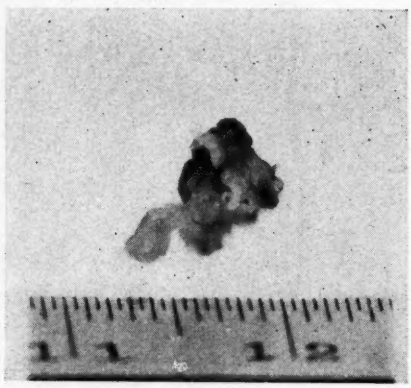

Fig. 5.

Fig. 3.—Intraductal growth, obstructing a milk duct, in a 47-year-old patient with bleeding from the nipple; no lump was present.

Fig. 5.—Photograph of the biopsy specimen taken from the same patient as that of Fig. 4.

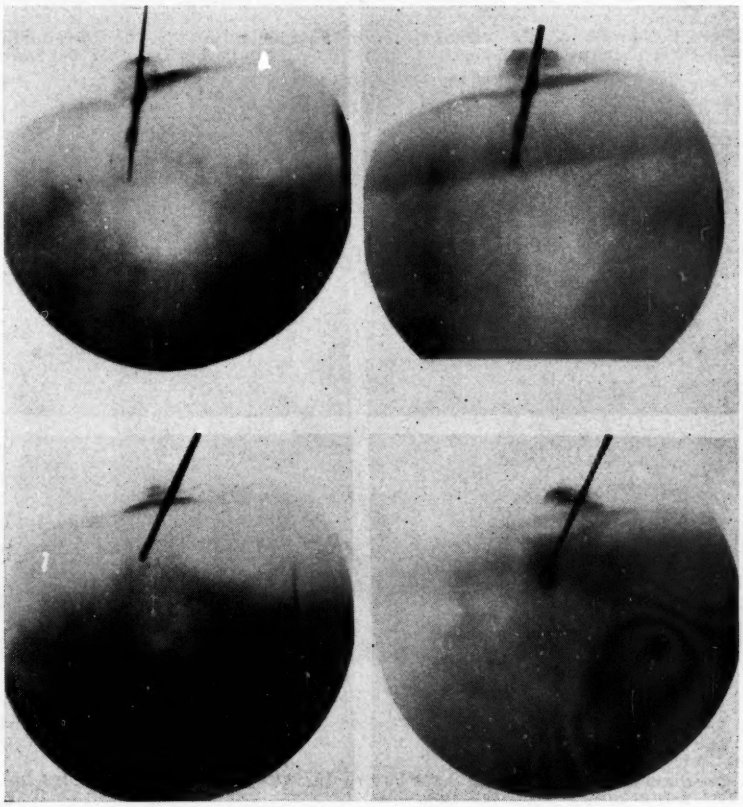

Fig. 4.—Three stages in the dilatation of a ductal orifice and insertion of the wire loop for the biopsy; continuation of the preceding case.

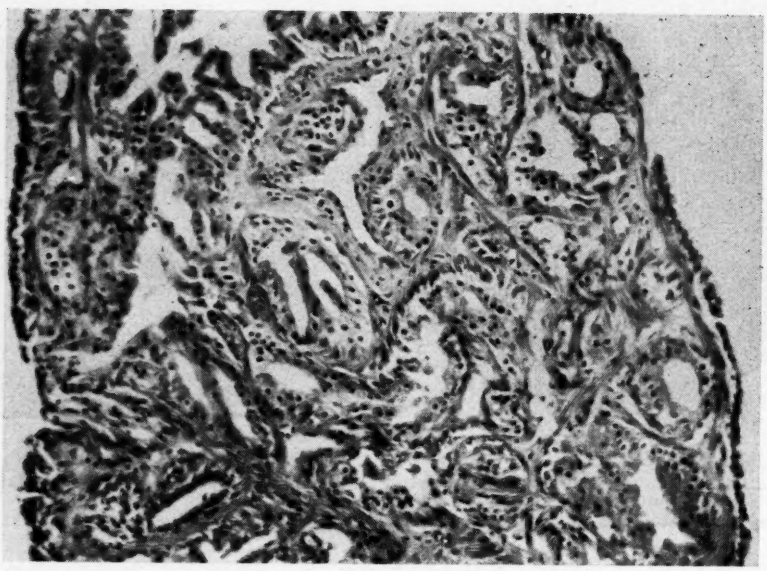

Fig. 6.—Microphotograph of the same specimen as shown in Fig. 5; intraductal fibroadenoma with malignant transformation. (Histologic study by Dr. Pou de Santiago.)

Fig. 7.

Fig. 8.

Fig. 7.—Partial mastectomy performed by Professor H. May, on patient of Figs. 3 to 6. The pathologic study by Professor Carlos M. Dominquez proved the existence of a malignant intraductal tumor.

Fig. 8.—Sixteen-year-old patient with a five-day bleeding from the nipple; no tumor was present. The x-ray shows a dilated milk duct and multiple annular images that correspond to the opaque substances disposed around the endocystic growth-image of papillary carcinoma. An intraductal biopsy was taken.

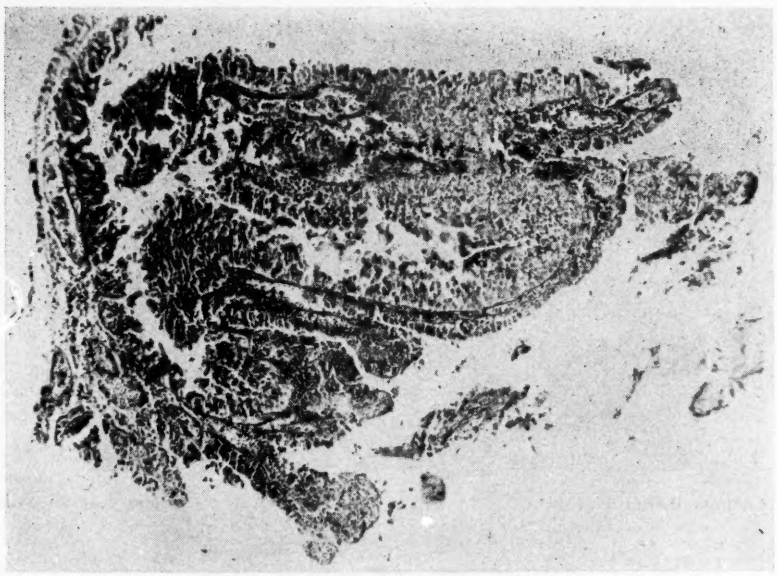

Fig. 9.—Microphotograph of the biopsy specimen from the patient shown in Fig. 8; intraductal fibroadenoma with malignant transformation. (Histologic study by Professor Carlos M. Dominguez.)

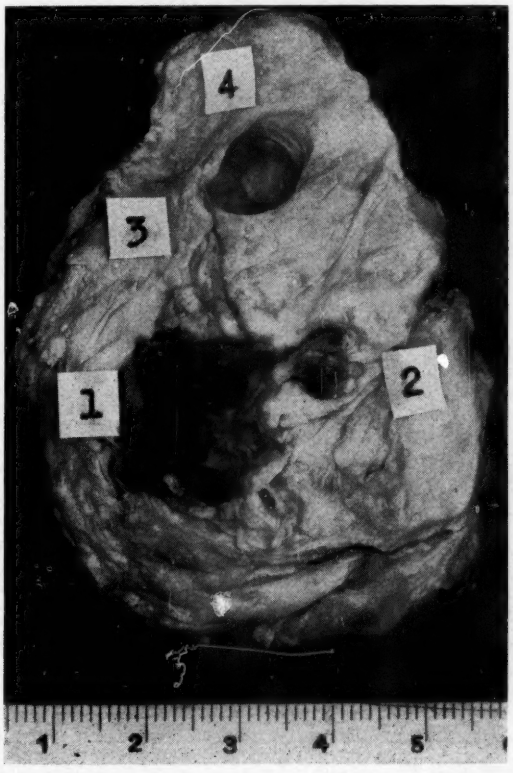

Fig. 10.—Mastectomy performed by Professor Julio Nin Y Silva on patient of Figs. 8 and 9. Pathologic study by Professor Carlos M. Dominguez: (1) Intracystic papillary fibroadenoma with malignant transformation; (2) smaller tributary ducts of the larger cystic cavity invaded at their source by the tumor; (3) milk duct that continues at (4), section showing the dilated milk duct unfolded at the base of the nipple.

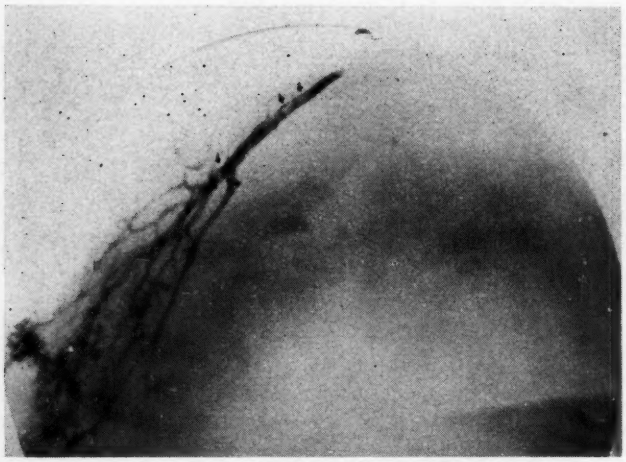

Fig. 11.—Various intraductal growths in a girl of 17 years, with a one-year bleeding from the nipple; no lump was present.

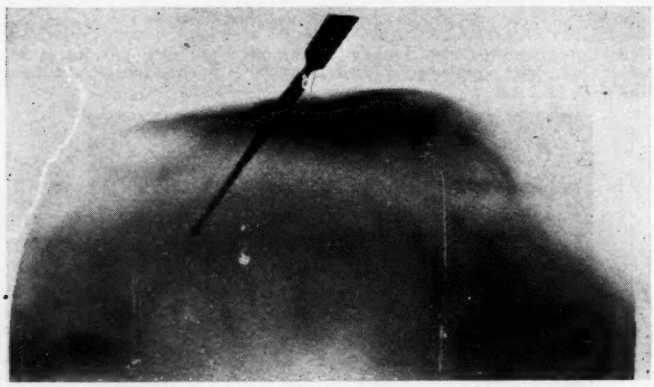

Fig. 12.—Taking the biopsy from the patient shown in Fig. 11.

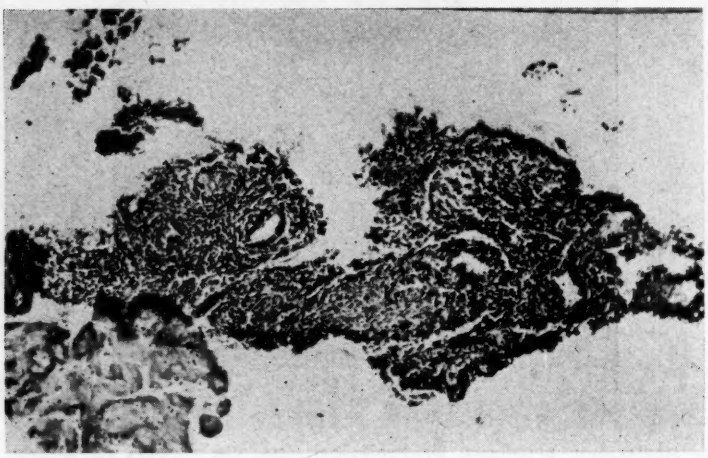

Fig. 13.—Topographic microphotograph of the endocanalicular biopsy specimen of the patient of Figs. 11 and 12; papillary and glandular fibroadenoma. (Pathologic study by Professor Carlos M. Dominguez.)

This method will often enable the surgeon to operate sooner in cancer of the breast, and to perform small, conservative, prophylactic operations in simple intraductal papillomas which have been well localized.

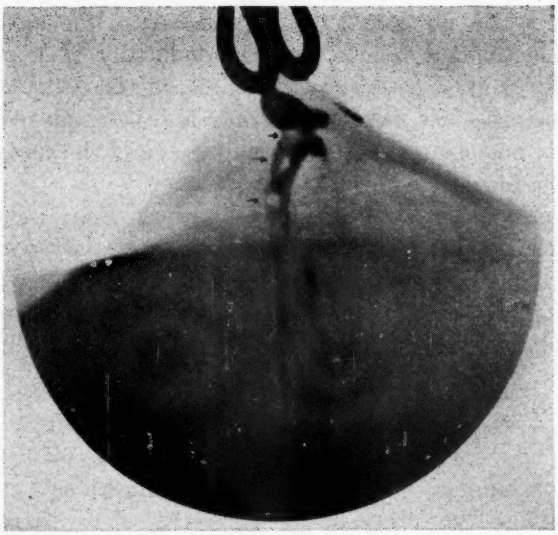

Fig. 14.—Various filling defects in a milk duct, caused by intraductal growths in a woman with a two-month bleeding from the nipple. There was an indurated milk duct with a small subareolar nodule.

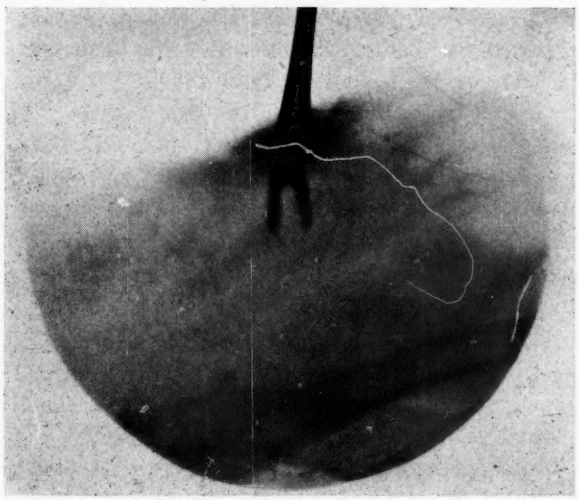

Fig. 15.

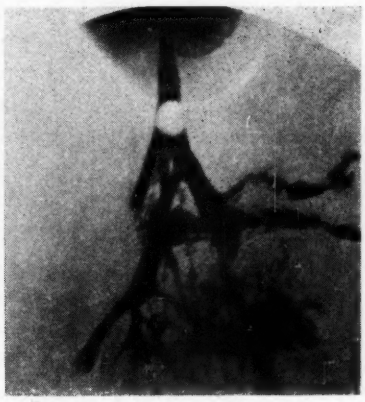

Fig. 16.

Fig. 15.—Introduction of a small forceps in the milk duct, in the same patient. Histologic study of the biopsy specimen by Professor Carlos M. Dominguez showed very extended fibroepithelial proliferation accompanied by abundant hemorrhage. The epithelial study revealed, in certain papillary formations, atypical cells and detachment of fusiform cellular sprouts. There were sufficient anatomic proofs to lead one to believe in the malignant transformation of the intraductal fibroadenoma.

Fig. 16.—Incorrect technique, when injecting opaque substance in a milk duct, may permit an air bubble and simulate an intraductal growth.

The pathologic process is localized exactly by introducing into the milk duct a fine metal catheter the extremity of which (by radiographic control) is put in contact with the lesion; then the surgeon can extirpate the corresponding region without searching for, or following, the milk duct. This localizes the site of the lesion, while Babcock's technique localizes the affected milk duct.

As to palpable tumoral lesions, there undoubtedly exist simpler ways of obtaining biopsies. But sometimes, as in high ductal obstructions caused by originally extraductal lesions, this method may also be employed, because, when well executed, it is innocuous, practically painless, and the x-rays aid in selecting the site for the biopsy.

It should be added that subsequent to this work, Felix Leborgne conceived the idea of performing an endocanalicular endoscopic study with simple implements devised and made by him, with which it was possible to obtain direct views of the ductal walls. The endoscopic pictures of the normal and pathologic ducts, as well as details of the instruments employed, will be described in a later article.

SARCOMA OF THE BREAST

With a Report of Thirty Cases

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(From the Breast Department of the Memorial Hospital for Cancer and Allied Diseases)

SARCOMA is a relatively uncommon neoplasm. The statistical studies of Williams and of Pack and LeFevre are instructive. The former, in an analysis of 13,824 primary neoplasms, found that 9.4 per cent were sarcomas. In 2,419 instances the breast was the site of the primary lesion and, of these, 3.9 per cent were sarcomas. Pack and Lefevre, in an analysis of 16,565 malignant tumors seen at the Memorial Hospital over a period of twelve years (1917 to 1929), concluded that sarcomas comprised 10.4 per cent of this total and that sarcoma of the breast formed only 0.64 per cent of all breast tumors.

There is considerable variation in the figures for the incidence of breast sarcoma given by different authors. Geist and Wilensky reported 3.9 per cent of all the breast tumors and 7.7 per cent of the malignant breast tumors in their cases to be sarcomas. Deaver and McFarland found 2 per cent of all the breast tumors in their series to be sarcoma. Fox stated that sarcoma represented 3 per cent of all the malignant breast tumors in his series and Hill and Stout reported 1.2 per cent as the incidence of sarcoma among the malignant breast tumors that they studied. The latter authors stated that if adenosarcoma were eliminated from their statistics, true sarcoma would comprise only 0.4 per cent of the malignant mammary growths in the series.

From 1926 to 1944 inclusive, 5,499 examples of malignant breast tumor were seen at the Memorial Hospital. Of these, thirty, or 0.5 per cent, were sarcomas. The higher percentage of sarcoma found by the earlier investigators may possibly be due to the inclusion of some small round-cell and spindle-cell neoplasms which, as Ewing has stated, were formerly classified as sarcomas but were in all probability atypical carcinomas.

Williams' statistics would also indicate that the relative liability of the female breast to sarcoma is much below the average for the body in general, 9.4 per cent of the body neoplasms being sarcomatous whereas only 3.9 per cent of female breast neoplasms are of this nature.

The infrequency of the involvement of the breast by sarcoma is further demonstrated by a review of the literature. In 1887, Gross collected 156 cases including 19 of his own, and in 1894, Williams found 99 examples of breast sarcoma in the material he studied. A most extensive survey undertaken by Geist and Wilensky, in 1915, disclosed 433 cases which had been reported since 1858, to which they added 22 of their own. D'Aunoy and Wright, in 1930, and Schreiner and Thibaudeau, in 1932, collected additional examples bringing the total up to 510. Since then, in addition to a number of isolated cases in

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the literature, there have been several relatively large series reported (Fox, Rose, Sailer, Rogers and Flo, and Hill and Stout).

The thirty examples of breast sarcoma seen at the Memorial Hospital since 1926 are herewith reported. Since treatment and prognosis are the primary considerations of the surgeon, the emphasis in the present investigation is on these aspects of the subject. The types of sarcoma encountered in the breast, which are to be discussed in the following pages, are enumerated in Table I.

TABLE I. SARCOMA DISCUSSED IN THIS REPORT*

TYPE	NUMBER
Cystosarcoma phyllodes (malignant)	4
Adenosarcoma	1
Fibrosarcoma	2
Spindle-cell sarcoma	5
Angiosarcoma	3
Liposarcoma	4
Lymphosarcoma	7
Hodgkin's sarcoma	2
Carcinosarcoma	1
Myosarcoma	1
Total	30

*Since this report was prepared, three additional cases of cystosarcoma phyllodes undergoing malignant changes in the stroma have been encountered as well as another example of adenosarcoma.

The sarcomas found in the breast consist of an admixture of epithelial and connective tissue. The epithelial elements are derived from the cells lining the ducts and acini, whereas the mesodermal component originates in either the connective tissue lying beneath the epithelial cells, the subepithelial connective tissue, or in that surrounding the ducts and acini, the pericanalicular and periacinar connective tissue. Hyperplastic changes in the subepithelial connective tissue may give rise to the so-called intracanalicular fibroadenoma, whereas hyperplasia involving the supporting connective tissue between the ducts produces the pericanalicular fibroadenoma.

It is accepted by numerous investigators that many sarcomas and an occasional carcinoma may arise on the basis of a previously existent fibroadenoma. In the course of the development of some sarcomas, the connective tissue elements may obliterate the epithelial components producing an almost pure sarcoma such as the fibrous and spindle-cell varieties. In others the epithelial elements may persist and both structures may manifest malignant characteristics, as in cystosarcoma phyllodes and adenosarcoma. The sarcomas containing both ectodermal and mesodermal constituents will be considered first.

CYSTOSARCOMA PHYLLODES

Cystosarcoma phyllodes was first described as a neoplastic entity by Johannes Müller in 1838. In its advanced state it is a huge freely movable tumor which may be cystic in part or solid with small clefts here and there into which project polypoid excrescences (Fig. 1). According to Lee and Pack this tumor develops from a previously existent fibroadenoma, probably of the intracanalicular variety. Lactation may be a factor in initiating this metamorphosis. The history is usually that of a pre-existent nodule which, after many

years of inactivity suddenly begins to increase in size. In some instances this is apparently initiated by trauma. Pain and ulceration may occur in the late stages after the tumor has become very large.

This neoplasm is usually benign but in some instances a true sarcomatous transformation takes place characterized by stroma proliferation, the presence

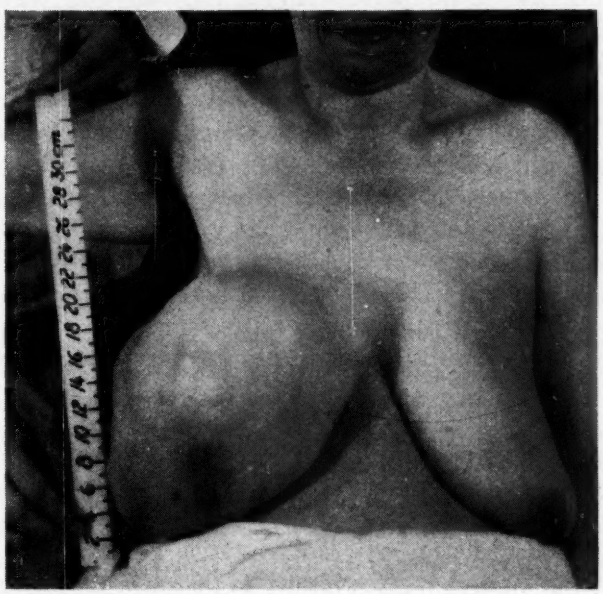

Fig. 1.—Cystosarcoma phyllodes.

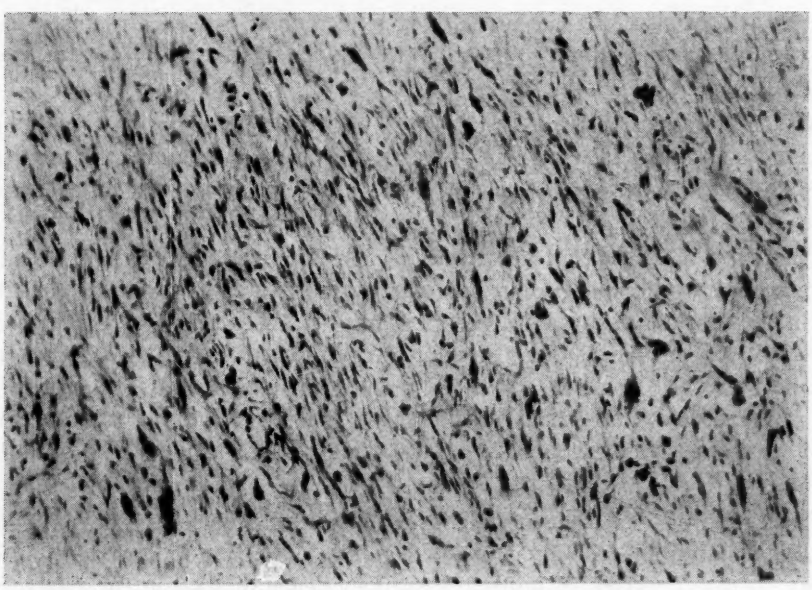

Fig. 2.—Photomicrograph of cystosarcoma phyllodes showing stroma proliferation, mitotic figures, and atypical cells (×340).

of mitotic figures, and of atypical cells (Fig. 2). In other instances there may be a metaplasia of the stroma resulting in myxomatous change or occasionally in squamous metaplasia with the formation of epithelial pearls.

Although these tumors are of low-grade malignancy, local recurrences and even distant metastases with fatal termination are sometimes encountered. Examples of this have been observed (Prym, Sophian, and White). Recently Cooper and Ackerman reported a unique case in which the axillary nodes were involved by metastasis of the connective tissue component.

During the period of 1926 to 1944, inclusive, there were seen at the Memorial Hospital forty-five examples of cystosarcoma phyllodes of which four, or 8.8 per cent, revealed sarcomatous metamorphosis. The metaplasia involved only the connective tissue. Of these patients with malignant deviation of the lesion, two underwent simple, and two radical, mastectomy. One of the latter patients was free of disease seven and one-half years after operation and the other was free of disease when last seen one year after mastectomy. Of the patients who underwent a simple mastectomy, one was lost to follow-up and the other was apparently free of disease one year after operation.

ADENOSARCOMA

Adenosarcoma is the malignant variant of fibroadenoma composed of both epithelial and connective tissue elements which is thought to arise in the pericanalicular variety. Many of these tumors result from the transformation of a long-standing fibroadenoma in which gestation, lactation, or trauma may have been an initiating factor. The history is that of a rapidly growing tumor which may ultimately occupy most of the breast. These tumors may be rounded or lobulated and composed of solid or cystic elements, some of the latter often attaining a huge size. In the initial stages the tumor is well circumscribed but as growth progresses it may spread out into the breast and fungate through the skin.

Although the microscopic structure is varied, the majority of these tumors are composed of spindle cells surrounding the acini and ducts. The epithelial component may manifest growth activity in the early phases but it is later, for the most part, obliterated by the connective tissue elements.

This type of neoplasm, according to Ewing, is highly malignant and although remissions have been observed the course is usually progressive with, in many instances, a rapidly fatal termination. As the tumor grows it involves the overlying skin, the pressure causing ulceration and necrosis with consequent sepsis and death. In some instances a fatal termination of the disease may result from metastasis. Local recurrences after removal of the tumor are frequent and, as Finsterer has shown, they may take the form of a spindle-cell sarcoma.

There was one example of adenosarcoma in this series. The patient was treated by simple mastectomy and low axillary dissection followed by a course of x-ray therapy. After remaining free of evidence of disease for twelve years she developed pulmonary metastases, proved by bronchoscopy, and died.

FIBROSARCOMA AND SPINDLE-CELL SARCOMA

Among our patients, as with those of other investigators, the fibrosarcomas and spindle-cell sarcomas constituted the numerically largest group. In the present series seven cases, or 23 per cent of the total, were in that category. In the experience of other observers these tumors constitute from 25 to 70 per cent of all breast sarcomas. Fibrosarcoma and spindle-cell sarcoma may arise in any location where there is supporting connective tissue. In addition, they may originate in the breast from a pre-existent fibroadenoma. The fibrosarcomas are relatively benign, whereas the spindle-cell tumors vary considerably in their degree of malignancy. Those composed of small cells are slower growing, relatively benign, and approach in structure and clinical features the fibrosarcomas.

Those composed of large cells exhibit more active growth, are softer, more vascular, tend to ulcerate and become necrotic. They metastasize and are prone to local recurrence. As this type of tumor grows it may infiltrate the surrounding tissues and structures, frequently penetrating blood vessels, thus producing metastases. These tumors grow relatively slowly in comparison with other forms of breast sarcoma and do not reach a large size.

In our series there were five spindle-cell sarcomas and two fibrosarcomas. All appeared to be of low-grade malignancy. One of the fibrosarcomas and one of the spindle-cell sarcomas were thought to have had their origin in a pre-existent fibroadenoma. The operative procedure in these cases was a simple mastectomy or local excision of the tumor, except in one instance in which a radical mastectomy was performed. This patient died six months after operation. One of the patients subjected to a simple mastectomy developed recurrences in the chest wall, dying five months after operation. One patient, treated by irradiation because she refused surgery, was lost to follow-up. The end result for this group of cases is shown in Table II.

Although not arising in the breast, two unusual examples of connective tissue tumors appearing in this organ are briefly mentioned here. The first was

TABLE II. COMPARISON OF THE RESULTS FOLLOWING RADICAL AND CONSERVATIVE SURGERY FOR FIBROSARCOMA AND SPINDLE-CELL SARCOMA ON THE BASIS OF FIVE-YEAR SURVIVAL

AUTHOR	RADICAL MASTECTOMY		SIMPLE MASTECTOMY OR LOCAL EXCISION		AXILLARY NODE INVOLVEMENT	
	ALIVE	DEAD	ALIVE	DEAD	ALIVE	DEAD*
Adair and Herrmann		1	4	1		
Boldrey	1		1			
Finsterer		1	3	2		1
Fox	9	4	5	6	1‡	1
Hill and Stout	1	2	1	1		
Rogers and Flo	3		6	3		
Sailer	1	3				1
Schreiner and Thibaudeau	1	1		2		
Warren and Meyer	1†	1				
Total	17	13	20	15	1	3

*All deaths with node involvement occurred within twelve months following surgery.
†Alive six years but has recurrent nodules and liver has begun to enlarge.
‡No follow up.

that of a 60-year-old woman with a soft, freely movable tumor 2 cm. in diameter in the right breast, of one week's duration. A radical mastectomy was performed. The tumor was found to lie immediately over the pectoralis muscle and to infiltrate it. The microscopic diagnosis was spindle-cell sarcoma, probably fascial—nodes clear.

The second case was that of a 32-year-old woman who, a few months after the birth of her only child, noticed a lump in the upper inner quadrant of the left breast. This increased in size over a period of eight months, at which time it measured about 2 cm. Skin dimpling could be developed over it. One small node was palpable in the left axilla. At operation a firm mass extending into the underlying pectoralis muscle was found which was widely excised with the surrounding muscle tissue. The microscopic diagnosis was desmoid. In so far as it is not unusual to encounter areas of fibrosarcomatous and myxosarcomatous transformation in desmoids (Pack and Ehrlich), the case is mentioned although no sarcomatous changes were noted in this example.

ANGIOSARCOMA

Blood vessel tumors, although a relatively common type of neoplasm, rarely undergo malignant deviation. An occasional angioma may metastasize following trauma, but according to Geschickter and Keasby less than 1 per cent of benign angiomas subjected to treatment manifest malignant changes.

Angiomas associated with metastases fall into three groups. In the first the primary lesion may be benign and produce benign-appearing metastases (Borrmann). In the second group an apparently benign angioma gives rise to malignant metastases (Robinson and Castleman). The third group comprises those cases in which the initial lesion, as well as the metastases, exhibits malignant characteristics (DaCosta, and Menville and Bloodgood). It is thought by some observers that those instances in which both primary and metastatic foci appear benign are really examples of a multicentric origin rather than of a metastatic phenomenon.

The clinical history of breast angiosarcoma is that of a tumor which, in the course of a few months, grows to a large size. Occasionally a purplish hue is imparted to the skin by the underlying tumor but usually there are no characteristic physical features associated with this neoplasm. The youth of the patient is suggestive although this neoplasm has been reported in elderly people.

In our series there were three examples of angiosarcoma, one of which is illustrated by Figs. 3 and 4. The ages of these women were 21, 23, and 26 years, respectively, an average of 23 years and 4 months. One patient underwent a radical mastectomy, one a simple mastectomy, and the third a local excision of the tumor. All died of the disease. The progress in this disease is relatively rapid, the average duration of life after operation in our patients being twenty-eight months. The two patients reported by Rogers and Flo died six months and two years, respectively, following simple mastectomy. In the cases reported by Hill and Stout the patients succumbed soon after operation, one three

months after simple mastectomy and the other about six weeks following a radical procedure. It would appear that metastasis occurs early. In two of our patients this phenomenon was encountered six and eight months, respectively, after the removal of the tumor. In one case reported by Hill and Stout metastatic disease appeared in the lungs one month after radical mastectomy.

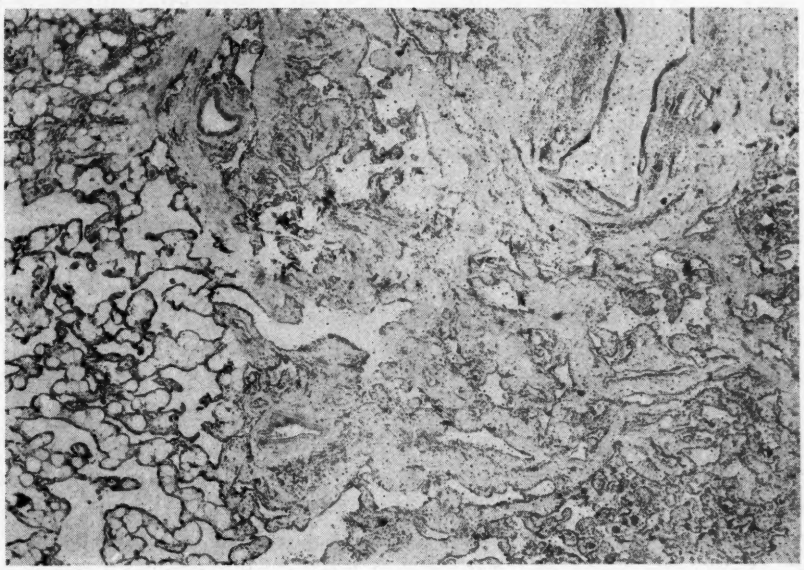

Fig. 3.—Photomicrograph of angiosarcoma; at the upper right a breast duct may be seen, at the left is normal-appearing angioma, and at the right angiosarcoma (×80).

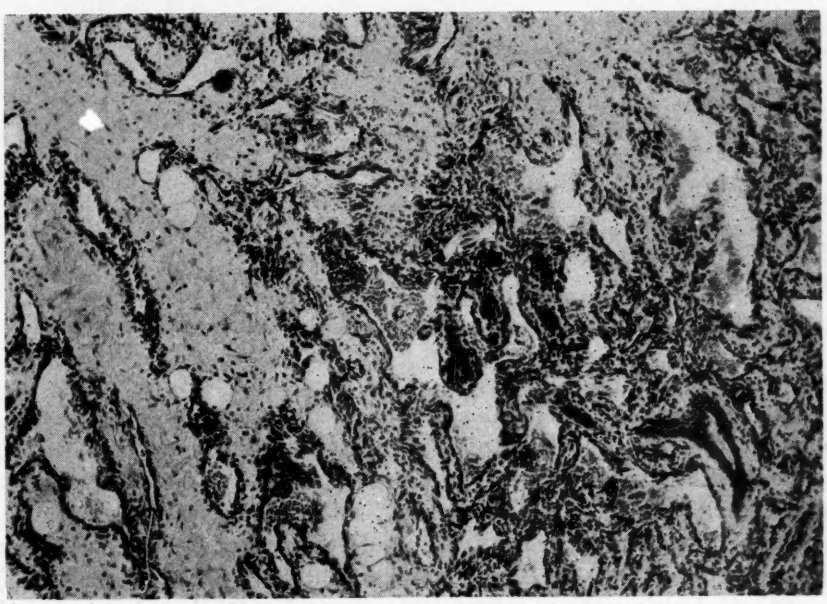

Fig. 4.—Higher magnification of the area of angiosarcoma shown in the preceding photograph (×300).

Geschickter mentioned two cases, one with axillary node invasion in a 53-year-old woman and the other with widespread metastasis in an elderly woman. On the other hand, the patient of Menville and Bloodgood, a 53-year-old woman, lived 10 years without evidence of the disease, following a radical mastectomy.

Many of the symptoms encountered in the course of this disease are due to hemorrhage from the metastatic foci. One of our patients developed hemiplegia and, some time later, an abdominal crisis associated with abdominal pain, rigidity, and shock, from which she did not recover. These phenomena were undoubtedly the result of hemorrhage from metastatic foci. The second patient developed pulmonary metastases and the third, metastases to the spine, pelvis, femur, sternum, and liver. Because it is a blood vessel tumor, metastasis by the vascular route in all probability occurs early and for that reason the prognosis is poor. Internal hemorrhage is frequently the cause of death.

LIPOSARCOMA

Liposarcoma is encountered most frequently in the retroperitoneal fat and in the extremities but it may be found in other parts of the body. Its occurrence in the breast, however, is unusual. Lifvendahl, in 1930, reported a fatal case occurring in a lactating woman. He was unable to find any other reported case of breast liposarcoma. Schultz-Brauns (1933) remarked on the rarity of the condition and Fox, in 1934, included one example of breast liposarcoma in his report of sixty mammary sarcomas. The patient was free from evidence of disease six months after a radical mastectomy. Geschickter (1940) mentioned three liposarcomas of the breast but gave no details.

Fig. 5.—Gross appearance of liposarcoma of the breast.

There were four instances of this variety of sarcoma in our present series. The gross and microscopic appearance of one of these tumors is shown in Figs. 5 and 6. One patient with a grade 4 liposarcoma had associated lymphatic leucemia. She was free of evidence of sarcoma four months after a radical mastectomy. The others were myxoliposarcomas of low-grade malignancy. One underwent a simple mastectomy followed by numerous recurrences over a period of ten years. She died ultimately of pulmonary metastasis. Of the other two patients, one had a local excision of the tumor, the other a radical mastectomy, and both have been free of disease four and four one-half years, respectively.

Seids and McGinnis believed that the high degree of malignancy of retroperitoneal liposarcoma may be due to the technical difficulties of removing all of the surrounding fat. If that be valid then the prognosis should be better for liposarcoma of the breast because here the lesion and contiguous fat are better circumscribed and readily extirpated with the breast.

LYMPHOSARCOMA AND HODGKIN'S SARCOMA

During the interval covered by the present survey, seven instances of primary lymphosarcoma of the breast were encountered at the Memorial Hospital. There is nothing characteristic about the lesion in this location by which a preoperative diagnosis can be established, although aspiration biopsy in some cases is suggestive. Clinically, the lesion resembles carcinoma. A radical mastectomy was performed in three instances, a simple mastectomy in one, and a local excision in the others. All patients were alive and free from disease over periods ranging from several months to seven years. Some of these cases have been reported in detail elsewhere (Adair and Herrmann).

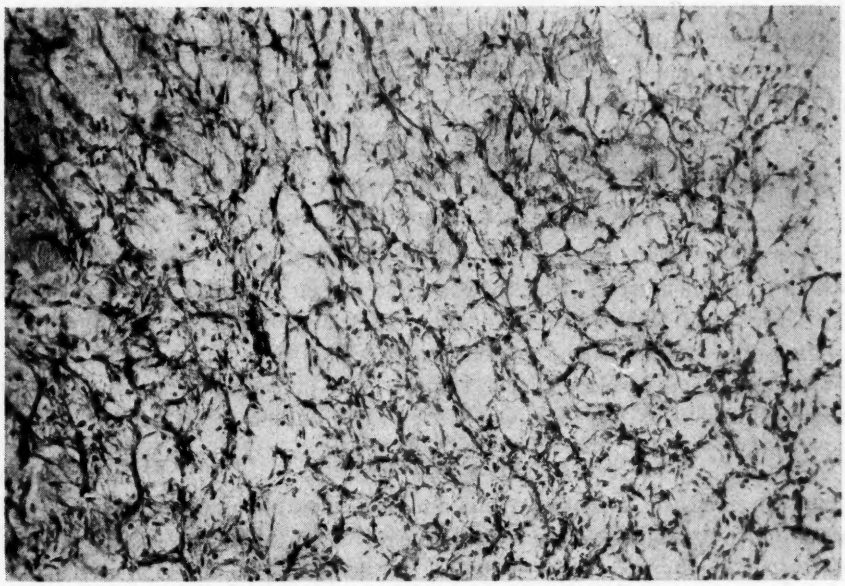

Fig. 6.—Photomicrograph of liposarcoma (×240).

Also during this period two patients with probable primary Hodgkin's disease of the breast were studied and have been described in another communication (Adair, Craver, and Herrmann).

CARCINOSARCOMA

This neoplasm is composed of both carcinoma and sarcoma. A number of examples have been reported. There was one in the present group of cases. Several theories have been advanced to explain the presence of carcinoma and sarcoma in the same neoplasm:

1. That it is a mixed tumor.
2. That a carcinoma stimulates the adjacent connective tissue to undergo sarcomatous transformation or, conversely, that an antecedent sarcoma causes a carcinomatous change in the neighboring epithelial elements.
3. That there are two distinct and separate tumors which grow toward each other and coalesce.
4. That the lesion is a primary carcinoma, some portions of which become so altered in histologic appearance that they are interpreted as sarcoma (Saphir and Vass).

Our patient had a small tumor in the breast for eighteen years, which for the last two years had grown rapidly. It was removed but recurred one and one-half years later. A modified radical mastectomy was then performed. It appeared on pathologic examination that the malignant process had its inception in a giant intracanalicular fibroadenoma. There was no lymph node involvement. She died of pulmonary metastasis five months after operation.

Other examples of sarcoma composed of more than one element are occasionally encountered in the breast. Two of these are the osteosarcoma and chondrosarcoma. Whether the osseous and cartilaginous foci arise from embryonic rests or as a result of metaplasia is a moot point. These tumors appear to be of relatively low-grade malignancy. There were no examples of these neoplasms in the present series.

MYOSARCOMA

Myosarcoma is an unusual tumor of the breast which may originate from smooth or striated muscle. Several cases have been reported (Bérard and associates, Leroux and Chanton, Geschickter, and Sailer). There was one example of an angiomyosarcoma in the present series. The therapeutic procedure in this instance was a local excision of the tumor. The subsequent course is unknown because the patient failed to report back to the clinic.

DIAGNOSIS

The diagnosis of breast sarcoma in most instances necessitates the differentiation of this condition from cyst or carcinoma. The history is frequently suggestive of sarcoma. In these instances the patient states that a tumor has been present, although quiescent, for a considerable length of time. Suddenly it begins to increase rapidly in size. This occasionally follows a trauma. A cyst may exhibit the same phenomena, although in the latter condition there is rarely the history of a pre-existent tumor. The spherical, cystic property of the mass and its capacity to transilluminate suggest that the tumor may be a cyst. Sarcoma is not translucent except in those forms of cystosarcoma phyllodes which are more cystic than solid.

Carcinoma may be suspected if there is skin dimpling or nipple retraction. These are seldom observed in sarcoma unless the tumor becomes so large that it impinges on the overlying skin. Then it may produce attachment, redness, and ulceration. Occasionally a diffuse duct carcinoma may produce great enlarge-

ment of the breast and in this respect simulate sarcoma. However, the diagnosis of sarcoma may be difficult or impossible to establish by clinical means. Aspiration biopsy in most instances will furnish the requisite information.

METASTASIS

Sarcomas are usually very vascular. Some of the blood vessels are present before the tumor undergoes sarcomatous transformation, but the greater number are newly formed to meet the requirements of the rapidly growing neoplasm. These channels are lined by a single layer of cells which is all that separates the lumen from the tumor. The neoplastic cells may penetrate the wall of the blood channel to form a parietal thrombus which may be broken off and carried as a tumor embolus to the lung to produce a metastatic focus. There is metastasis to distant organs in 12 to 18 per cent of the cases. In order of frequency these are lung, liver, brain, dura mater, pleura, mediastinal, retroperitoneal, and axillary nodes, heart, kidney, and bones (Geist and Wilensky, Cheatle and Cutler). In our series there were lung metastases from a carcinosarcoma, a spindle-cell sarcoma, a myxoliposarcoma, and an angiosarcoma. Another angiosarcoma metastasized to the bones and liver. Despite an apparent cure of a breast sarcoma it is possible for a metastatic focus to appear after many years. This, however, is an unusual phenomenon. Willis quoted several examples, all of pulmonary metastasis but from sarcoma other than mammary. In one of our patients, lung metastasis appeared twelve years after a simple mastectomy for spindle-cell sarcoma, the patient having remained free from evidence of the disease during the interim. Whenever long-delayed metastasis occurs under these circumstances it would seem that the secondary lesion must have had its inception before the local neoplasm was removed. After lying dormant for a lengthy period of time these cell emboli manifest growth activity for some reason, either stimulation or removal of inhibition.

Lymphatic channels have not been described in sarcoma. For this reason the lymphatic spread of the disease with invasion of the lymph nodes, except in lymphosarcoma, melanosarcoma, and carcinosarcoma, is necessarily a rare phenomenon.

Although axillary and supraclavicular lymph nodes may be palpable, the enlargement in most instances is the result of an inflammatory rather than a metastatic process. In our series four patients had palpable axillary nodes. Three underwent a radical procedure and no involvement of the nodes was found. There was a local excision of the tumor without removal of nodes in the fourth patient. In two additional patients with no palpable adenopathy, hyperplastic nodes were encountered at operation. Upon microscopic examination these were found to be free of disease.

Metastatic lymphatic spread in sarcoma, although infrequent, has been observed. Gross gave the incidence of axillary involvement as 0.64 per cent. Poulsen found axillary node disease in three instances among thirty-three patients, an incidence of 9 per cent. Geist and Wilensky in a collection of 435 cases found 3 per cent of the patients to have lymph node invasion. In Table III there has been assembled 678 examples of breast sarcoma taken from

TABLE III. LYMPH NODE INVOLVEMENT IN REPORTED CASES OF BREAST SARCOMA

AUTHOR	YEAR	NUMBER OF CASES	NUMBER WITH LYMPH NODE METASTASES
Geist and Wilensky	1915	435	13
D'Aunoy and Wright	1930	68	4
Sophian	1930	15	0
Schreiner and Thibaudeau	1932	7	0
Fox	1934	52	2
Rose	1936	15	1*
Sailer	1937	15	1
Harrington and Miller	1940	9	0
Hill and Stout	1942	10	0
Rogers and Flo	1942	22	1
Adair and Herrmann	1945	30	0
Total		678	22 (3.2%)

*Melanosarcoma.

the literature. No attempt has been made to collect all the individual case reports. Only the relatively large series have been included. It is seen that among this group there are twenty-two instances of lymph node metastasis, one of which was in association with a melanosarcoma. This does not mean that 3.2 per cent of the patients with breast sarcoma have lymph node disease but merely that in this collected series the reported examples of lymph node invasion constitute 3.2 per cent of the total number of reported cases. It is possible that the actual incidence of node involvement is smaller than appears from the figures because in some of the earlier examples the primary lesion may have been a round-cell or spindle-cell carcinoma which, as Ewing has stated, was frequently confused with sarcoma. Geist and Wilensky remarked that in their series most instances of lymph node involvement occurred with the round-cell type of tumor.

It is of interest that all of the patients with fibrosarcoma or spindle-cell sarcoma in whom lymph node metastasis was found, and in whom the progress of the disease could be determined (Table II), succumbed to the malady within one year after operation. Although no accurate conclusions can be derived from this small number of instances, it suggests that, if the axillary nodes are diseased, the prognosis is decidedly grave, much more so than in carcinoma of the breast with axillary metastasis. The explanation may be that the node involvement, as Stewart and Copeland have suggested for neurogenic sarcoma, is produced by venous tumor emboli. On that basis, metastasis to the nodes is merely one aspect of a general blood-borne dissemination of the neoplasm.

SURGICAL THERAPY

Many authors (Geist and Wilensky, Cheatle and Cutler, Deaver and McFarland, Rose) advocate radical mastectomy as the procedure most likely to produce the highest cure rate. In so far as it has been demonstrated that there are different varieties of sarcoma which vary in degree of malignancy and since there are variations within the individual groups, it would seem that such a sweeping conclusion is unwarranted.

In an endeavor to evaluate the efficacy of the surgical procedures employed in the treatment of sarcoma, sixty-five suitable cases of fibrosarcoma and spindle-cell sarcoma, were selected for analysis. These varieties were chosen

because they constitute the numerically largest group of sarcomas. Only those patients who were living and free from disease five years or longer after operation were chosen for comparison with those who had undergone surgery and died from the disease within that period. The compilation of such a group presents several difficulties. It the first place many cases are unsuitable because they are reported so soon after operation that there is no opportunity to know the postoperative course. In others the follow-up period is less than five years. Another difficulty encountered is that a great number of sarcomas were treated in the period before the radical procedure was introduced by Halstead (1893). Therefore, in order to evaluate this factor properly, only those patients who were treated after 1893 were considered.

The results have been tabulated (Table II). It is seen that of thirty patients who were subjected to radical mastectomy seventeen are alive and thirteen are dead, and of thirty-five who underwent a simple mastectomy or local excision twenty are alive and fifteen are dead. The parallelism between the number of deaths in the two groups (radical and simple mastectomy) is more significant than that of the survivals in the corresponding series for the following reason. The deaths all occurred within three years after operation, the majority within a much shorter period. The possibility for accurate follow-up is much greater over a relatively short period than it is for a longer one. Patients who have recurrence of the disease are much more likely to report back to the clinic than those who are well. Thus, the large majority of those who fail to return are undoubtedly free of disease and should be included among those cured by operation. When considered in this light the very small proportion of cured sarcomas in Table II loses its apparent significance. From this small series one cannot draw accurate conclusions but it does suggest that the simple mastectomy is as effective as the radical procedure in the treatment of fibrosarcoma and spindle-cell sarcoma.

As a further aid in evaluating the therapeutic procedure of radical mastectomy it was thought that the presence or absence of axillary node involvement in patients so treated might furnish an index. One hundred cases in which a radical mastectomy was performed were gathered from the literature. Only examples of lymphosarcoma, melanosarcoma, and carcinosarcoma were excluded because these forms of sarcoma behave like carcinoma and metastasize chiefly by way of the lymphatics. The collected cases have been tabulated according to authors (Table IV) and according to type (Table V). It is seen that 4 per cent of these patients had axillary node disease. Although the value for statistical analysis of this small series is limited, it would seem that lymph node involvement in breast sarcoma is too infrequent to justify the employment of radical surgery. Furthermore, some of the examples of lymph node involvement may be on the basis of mistaken diagnosis of the primary lesion and others may be the result of venous embolism. If there are tumor emboli in the blood stream, removal of the regional lymph nodes would seem to be of little value.

On the other hand, Warren and Meyer concluded from their studies of sarcoma in various anatomic locations that lymph node metastasis occurs in

TABLE IV. LYMPH NODE INVOLVEMENT IN ONE HUNDRED COLLECTED CASES OF BREAST SARCOMA; TREATMENT BY RADICAL MASTECTOMY

AUTHOR	NUMBER OF CASES	NUMBER OF CASES WITH AXILLARY NODE DISEASE
Adair and Herrmann	6	0
Bishop	2	0
Boldrey	1	0
D'Aunoy and Wright	4	0
Fox	23	2
Geist and Wilensky	11	1
Harrington and Miller	9	0
Hill and Stout	11	0
Menville and Bloodgood	1	0
Rhodenberg	6	0
Rogers and Flo	4	0
Rose	9	0
Sailer	7	1
Schreiner and Thibaudeau	2	0
Sophian	2	0
Sullivan	1	0
Wellbrock	1	0
Total	100	4

In a few instances in which the nodes were not mentioned it is assumed that they were uninvolved.

about 7 per cent of cases exclusive of melanosarcoma and lymphosarcoma. They believed that lymph node dissection in conjunction with radical removal of the sarcoma may improve the prognosis from 5 to 10 per cent and may be of value even after lymphatic metastasis is clinically evident. This is not substantiated for breast sarcoma by the present investigation.

There are, however, three types of breast sarcoma in which radical mastectomy appears to be indicated. One is the so-called carcinosarcoma, another is melanosarcoma, and the third, as we have suggested in a previous communication, is lymphosarcoma primary in the breast. In lymphosarcoma and melanosarcoma the mode of spread is thought to be almost entirely by way of the lymphatics.

TABLE V. TYPES OF SARCOMA AND ASSOCIATED LYMPH NODE INVOLVEMENT IN 100 CASES; TREATMENT BY RADICAL MASTECTOMY

TYPE OF SARCOMA	NUMBER OF CASES	NUMBER WITH LYMPH NODE INVOLVEMENT
Fibrosarcoma	44	3
Spindle-cell	12	
Adenofibrosarcoma	9	
Cystosarcoma	7	
Liposarcoma	4	
Round-cell	4	1
Unknown	4	
Neurogenic	3	
Angiosarcoma	3	
Perithelioma	3	
"Sarcoma"	3	
Polymorphous cell	2	
Osteochondrosarcoma	1	
Giant cell	1	
Total	100	4

In carcinosarcoma the epithelial component may metastasize to the regional nodes as it does from carcinoma of the breast. In Smithy's collected group of thirty-three cases, twelve, or 36 per cent, revealed axillary node metastasis of the epithelial element. This approximates the figure (33 per cent) that Harrington and Miller gave for the incidence of axillary node involvement in cases of breast cancer with no palpable axillary nodes.

Aside from the exceptions just noted, we believe from the available evidence that conservative surgery in breast sarcoma produces as satisfactory a result as does the radical procedure with none of the disadvantages of the latter. Since there is evidence that breast sarcoma owes its inception in some instances to malignant deviation of a fibroadenoma this tumor should be removed early. Early removal is also the best method for preventing metastatic spread if sarcomatous change has already occurred. If the tumor is small and of low-grade malignancy, simple excision should suffice. If larger or of a higher degree of malignancy a simple mastectomy with removal of the pectoral fascia is indicated. The more malignant forms have the tendency to infiltrate the underlying muscle and give rise to recurrences. For that reason, in situations where there is evidence of this possibility the pectoralis major muscle should be removed. Fox advocated removal of both pectoral muscles in all cases but omitted an axillary dissection. Geschickter, on the other hand, favored simple mastectomy with the removal of the pectoralis fascia in the treatment of fibrosarcoma and spindle-cell sarcoma.

It is of interest that the present-day conclusions concerning the surgical treatment of breast sarcoma coincide with those arrived at by Gross before the era of radical surgery. In 1887 he wrote, "The entire breast along with any skin that may be invaded must be extirpated, especial care being paid to the complete removal of every particle of paramammary fat and the fascia of the pectoralis muscle, in which tissues experience shows that recurrence takes place."

RADIATION THERAPY

The radiosensitivity of tumors varies. Among sarcomas the lymphosarcoma and Hodgkin's sarcoma are relatively sensitive. Liposarcomas also show some sensitivity but there is considerable variability. The types composed of young fat cells and those that contain mucoid and myxosarcomatous areas tend to be relatively sensitive to large doses of x-rays. Those composed mainly of adult spindle cells are more resistant.

Since breast sarcoma is an unusual lesion there has been relatively little opportunity to determine the therapeutic effect of irradiation on these tumors. Wintz reported thirteen patients, most of them with spindle-cell sarcomas treated by this modality. Four received preoperative x-ray therapy and then underwent a cautery excision of the tumor. In addition, three of these individuals were subjected to x-ray castration. These patients were alive after twenty, thirteen, and seven years, respectively. The fourth, or noncastrated patient, was free of disease for two years, at which time she became pregnant. In the first month of the pregnancy she developed a recurrent nodule in the breast followed soon

after by widespread skin nodules, lung metastasis, and death. Wintz believed it significant that this patient was not castrated.

One patient was subjected to a radical mastectomy followed by x-ray therapy. Two years later she developed a recurrence and died shortly thereafter of lung metastasis. Four inoperable tumors were treated by irradiation, all of the patients dying within two years following initiation of this therapy. Of four patients with recurrence after operation treated by irradiation, three died within the first year and the other during the second year postirradiation.

Wintz concluded that preoperative irradiation is of value in those instances in which the sarcoma is confined to the breast but that x-ray therapy is useless in those cases in which the process has spread beyond its confines or in recurrent disease.

Some investigators have reported favorable results from irradiation. Pfahler was enthusiastic about this agent especially in the treatment of recurrences. It is possible, however, that in some of the instances in which spectacular regression of the lesion is achieved the neoplasms may be lymphosarcoma or small cell carcinoma.

Geschickter believed that for liposarcoma, irradiation is preferable to radical surgery but that at best the disease can only be arrested, not cured. He advocated irradiating the regional lymph node areas as well as the breast because of the possibility of metastasis.

Lymphomatous involvement of the breast is infrequent but where it does occur it is usually as a local manifestation of a generalized disease process. Under these conditions palliative x-ray therapy is the treatment of choice.

Roentgen therapy was administered to six of our patients. Two individuals with fibrosarcoma and one with spindle-cell sarcoma were irradiated following simple mastectomy. They were all alive and free of disease for more than nine years after operation. One woman with a spindle-cell sarcoma received x-ray therapy and gold radon seeds but refused operation and was lost to follow-up.

One of our patients with angiosarcoma underwent a radical mastectomy and postoperative x-ray therapy. She died of pulmonary metastasis two years after the initial appearance of the breast tumor. Another woman with adenosarcoma underwent a modified radical mastectomy and postoperative high voltage roentgen therapy. She remained free of disease for twelve years, after which she developed lung metastasis and died.

From this small number of cases no accurate conclusions may be established. In those long-surviving patients whose lesion was a sarcoma of low-grade malignancy and in whom a simple mastectomy followed by irradiation were the therapeutic procedures, it is conceivable that surgery alone might have sufficed. This reasoning may also apply in the three cases of preoperative irradiation followed by local excision reported by Wintz. In our two instances of highly malignant sarcoma the patients died of the disease despite radical surgery and associated x-ray therapy.

Postoperative x-ray treatment, however, may be of value in very cellular tumors and in those which manifest infiltrative tendencies. There is also a pos-

sibility that the vessels adjacent to the excised tumor or breast may contain tumor thrombi. Under these circumstances radiation therapy might prove advantageous.

It is quite possible that in some forms of breast sarcoma the incidence of recurrence and metastasis may be materially decreased by irradiation. Until enough data have been accumulated, a definite conclusion cannot be reached.

PROGNOSIS

The prognosis is dependent upon the variety of the neoplasm. Sarcoma is a generic term for a number of new growths which have in common their origin from mesodermal elements. These tumors vary in their malignant potentialities. At one end of the scale is the low-grade malignant variant of cystosarcoma phyllodes and at the opposite extreme is the highly malignant angiosarcoma. This classification is subject to further division because there are variations in degree of malignancy within the groups. Thus, prognosis depends not only on the type of sarcoma but also on the grade of the particular lesion within the group.

Age is also a factor. Sarcoma tends to occur in relatively young women. The average age for our patients was 45 years. Gross summarized the influence of age when he wrote, "Sarcoma occurring in a functionally active breast evinces a morbid disposition to recur after operation with less disposition to metastasize whereas a sarcoma of the declining breast recurs less frequently but it generalizes in a greater number of instances." This generalization does not appear to apply to angiosarcoma as evidenced by the rapid appearance of metastases in our youthful patients and those of similar age reported in the literature.

Local recurrence, regardless of the surgical procedure employed, is a frequent occurrence but does not necessarily imply a poor prognosis. For example, Riedel removed recurrent lesions six times over a period of twenty years, the patient exhibiting no evidence of disease at the time of death. A similar experience was reported by Gross. The latter stated that 50 per cent of the recurrences take place within the first six months and that they may appear as late as twenty-five years after the removal of the initial lesion. The high percentage of recurrences given by the earlier writers may have been due to the inclusion of atypical carcinomas among their sarcomas. There were recurrences in eight of the cases being reported. These occurred in the following classes: liposarcoma, spindle-cell sarcoma, carcinosarcoma, and all of the instances of angiosarcoma.

It has been frequently stated that sarcoma of the breast offers a better prognosis than carcinoma in this organ. This, as shown previously, depends upon the variety and grade of the sarcoma. Certainly angiosarcoma is much more malignant than most cancers and, conversely, low-grade fibrosarcoma and liposarcoma are much less malignant than low-grade carcinoma. For that reason a general statement is not valid and prognosis must be determined, not from the disease as a whole, but from an evaluation of each example on the basis of type and histologic grading. Lymph node involvement appears to have a much more serious implication in connection with breast sarcoma than the same phenomenon in association with breast cancer. Death may result from sepsis in those in-

stances where the primary lesion or recurrences break down and ulcerate. In some cases metastasis causes a lethal outcome, whereas in the angiosarcomas internal hemorrhage from a metastatic focus is frequently the cause of death.

SUMMARY AND CONCLUSIONS

1. Various types of sarcoma encountered in the breast are briefly described.

2. Thirty cases of breast sarcoma are reported, among which are three angiosarcomas.

3. A study of 100 radical mastectomies for sarcoma reveals lymph node invasion in 4 per cent.

4. An analysis of the results of surgical therapy would indicate that conservative procedures are as effective as radical measures.

5. Radical mastectomy is the procedure of choice in primary lymphosarcoma, melanosarcoma, and carcinosarcoma.

6. There are not enough data on irradiation of breast sarcoma by which to evaluate the efficacy of this therapeutic procedure.

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REFERENCES

Adair, F., Craver, L., and Herrmann, J.: Hodgkin's Disease of the Breast, Surg., Gynec. Obst. **80**: 205, 1945.

Adair, F., and Herrmann, J.: Primary Lymphosarcoma of the Breast, SURGERY **16**: 836, 1944.

Bérard, L., Martin, J. F., and Henry, M.: A propos d'un cas de myosarcome mammaire, Lyon chir. **34**: 602, 1937.

Bishop, E.: Sarcoma of the Breast, J. M. A. Georgia **30**: 232, 1941.

Boldrey, E.: Primary Sarcoma of the Breast, Canad. M. A. J. **35**: 17, 1936.

Borrmann, R.: Metastasenbildung bei histologisch gutartigen Geschwülsten (Fall von metastasierendem Angiom), Beitr. z. path. Anat. u. z. allg. Path. **40**: 372, 1906.

Cheatle, L., and Cutler, M.: Tumors of the Breast, Philadelphia, 1932, J. B. Lippincott Company.

Cooper, W., and Ackerman, L.: Cystosarcoma Phyllodes With a Consideration of Its More Malignant Variant, Surg., Gynec. & Obst. **77**: 279, 1943.

DaCosta, J.: A Case of Endothelioma of the Mammary Gland, Am. Med. **5**: 1024, 1903.

D'Aunoy, R., and Wright, R.: Sarcoma of the Breast, Ann. Surg. **92**: 1059, 1930.

Deaver, J., and McFarland, J.: The Breast, Anomalies, Diseases and Treatment, Philadelphia, 1917, The Blakiston Company.

Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, 1940, W. B. Saunders Company, p. 555.

Finsterer, J.: Ueber das Sarkom der weiblichen Brustdrüse, Deutsche Ztschr. f. Chir. **86**: 352, 1907.

Fox, S.: Sarcoma of the Breast, Ann. Surg. **100**: 401, 1934.

Geist, S., and Wilensky, A.: Sarcoma of the Breast, Ann. Surg. **62**: 11, 1915.

Geschickter, C.: Diseases of the Breast, Philadelphia, 1943, J. B. Lippincott Company, p. 379.

Idem: Treatment of Lipomas and Liposarcomas. In Pack, G., and Livingston, E., Treatment of Cancer and Allied Diseases, vol. 3, New York, 1940, Paul B. Hoeber, Inc., p. 2104.

Geschickter, C., and Keasby, L.: Tumors of Blood Vessels, Am. J. Cancer **23**: 568, 1935.

Gross, S.: Sarcoma of the Female Breast, Am. J. M. Sc. **94**: 2, 1887.

Harrington, S., and Miller, J.: Fibrosarcoma of the Mammary Gland, SURGERY **7**: 129, 1940.

Idem: In Pack, G., and Livingston, E.: Treatment of Cancer and Allied Diseases, vol. 1, New York, 1940, Paul B. Hoeber, Inc., p. 709.

Hill, R., and Stout, A.: Sarcoma of the Breast, Arch. Surg. **44**: 723, 1942.

Lee, B. J., and Pack, G. T.: Giant Intracanalicular Fibro-Adenomyxoma of the Breast. The So-Called Cystosarcoma Phyllodes Mammae of Johannes Müller, Am. J. Cancer **15**: 2583, 1931.

Leroux, R., and Chanton, M.: Dysembryone Complexe de la Glande Mammaire, Bull. Asso. Franc. Étude Cancer **22**: 80, 1931.

Lifvendahl, R.: Liposarcoma of the Mammary Gland, Surg., Gynec. & Obst. **50**: 81, 1930.

Menville, J., and Bloodgood, J.: Subcutaneous Angiomas of the Breast, Ann. Surg. **97**: 401, 1933.
Müller, J.: Ueber den feinern Bau und die Formen der krankhaften Geschwulste, Berlin, 1838, G. Reimer, p. 56.
Pack, G. T., and Ehrlich, H. E.: Neoplasms of the Abdominal Wall With Special Consideration of Desmoid Tumors, Internat. Abstr. Surg. **79**: 177, 1944.
Pack, G. T., and LeFevre, R.: The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, J. of Cancer Research **14**: 167, 1930.
Pfahler: Quoted by Deaver and McFarland, p. 432.
Poulsen, K.: Die Geschwülste der Mämma, Arch. f. klin. Chir. **42**: 593, 1891.
Prym, P.: Fibrocystadenoma Sarkomatosum der Mämma mit Metastasen, Frankfurt. Ztschr. f. Path. **10**: 60, 1912.
Rhodenberg, G.: Sarcoma of the Breast. A report of 6 cases, Proc. N. York Path. Soc. **17**: 112, 1917.
Riedel: Quoted by Cheatle and Cutler.
Robinson, J., and Castleman, B.: Benign Metastasizing Hemangioma, Ann. Surg. **104**: 453, 1936.
Rogers, H., and Flo, S.: Sarcoma of the Breast, New England J. Med. **226**: 841, 1942.
Rose, J.: Die Sarkome der Weiblichen und die Geschwülste der mannlichen Brustdrüsen nach dem Material der chirurgischen Klinik zu Leipzig, Deutsche Ztschr. f. Chir. **246**: 151, 1936.
Sailer, S.: Sarcoma of the Breast, Am. J. Cancer **31**: 183, 1937.
Saphir, O., and Vass, A.: Carcinosarcoma, Am. J. Cancer **33**: 331, 1938.
Schreiner, B., and Thibaudeau, M.: Sarcoma of the Breast, Ann. Surg. **95**: 433, 1932.
Schultz-Brauns, O.: Die Geschwülste der Brustdrüse, in Lubarsch, O., und Henke, F., Handbuch der speziellen pathologischen Anatomie, und Histologie, vol. 7, pt. 2, Berlin, 1933, Julius Springer, p. 236.
Seids, J., and McGinnis, R.: Malignant Tumors of Fatty Tissues, Surg., Gynec. & Obst. **44**: 232, 1927.
Smithy, H.: Mixed Malignancy of the Breast, SURGERY **16**: 854, 1944.
Sophian, L.: Adenofibrosarcoma of the Breast, Arch. Path. **9**: 1007, 1930.
Stewart, F., and Copeland, M.: Neurogenic Sarcoma, Am. J. Cancer **15**: 1235, 1931.
Sullivan, S.: Osteochondrosarcoma of the Breast. Illinois M. J. **82**: 140, 1942.
Warren, S., and Meyer, R.: Lymph Node Metastasis of Sarcoma, Am. J. Path. **14**: 605, 1938.
Wellbrock, W.: Sarcoma of the Breast With Foreign Body and Tumor Giant Cells, Ann. Surg. **90**: 154, 1929.
White, W.: Malignant Variant of Cystosarcoma Phyllodes, Am. J. Cancer **40**: 458, 1940.
Williams, W.: The Varieties of Mammary Neoplasm and Their Relative Frequency, Brit. M. J. **2**: 576, 1892.
Idem: Diseases of the Breast, London, 1894, John Bale, Sons & Curnow, Ltd., p. 417.
Willis, R.: Spread of Tumors in the Human Body, London, 1934, J. & A. Churchill, Ltd., p. 114.
Wintz, P.: Die Röntgentherapie bei Ovarialsarkomen und Mammar-sarkomen, Univ. Internat. Contra Cancrum. Acta. **2**: 311, 1937.

A HISTOLOGIC CLASSIFICATION OF CARCINOMA OF THE BREAST*

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NO UNIFORMLY accepted modern classification of carcinomas of the breast now exists and any effort to construct one becomes an easy object of criticism. To satisfy the justly practical needs of the clinical surgeon and to appease all of the demands of the tumor morphologist together make this problem generally discouraging. Attitudes toward classification differ greatly from person to person and William Boyd, according to N. C. Foot,[1] has divided classifiers into "lumpers" and "splitters," the implications of which need no exposition. We are forced to admit that we employ both the device of lumping and that of splitting. In general, we prefer to split when sufficiently acquainted with particular types of tumors and to lump when the histologic and clinical characters of a group of tumors are not familiarly known or recorded.

With increasing emphasis on the recognition of cancer in its earliest phases, it seems desirable when possible to include in classification schemes a listing for noninfiltrating forms of carcinoma. Whereas the existence of these noninfiltrating forms is being increasingly accepted, there still remains a body of pathologists who will not make the diagnosis of carcinoma unless they detect infiltration. This is scarcely logical since it is so much more reasonable to conclude that if the tumor had not been a carcinoma prior to infiltration, then infiltration would not have occurred. In the classification scheme to follow, in so far as possible, the tumors have been classified as to site of origin and, hence, the nipple has been taken as a point of beginning, followed by tumors of ducts and lobules, and finally certain relatively rare or highly unusual histologic types have been enumerated. Comment as to the probable site of origin of these rare types will be made as each is discussed. The classification to be presented deals only with the various histologic types of mammary carcinoma. Certain forms of mammary cancer such as carcinoma en cuirasse and inflammatory carcinoma are omitted since they do not have histologic specificity. Benign tumors of the breast proper are not to be discussed. It is not one of the purposes to include tumors of the skin of the breast and its appendages or the various tumors of the soft somatic tissues, since these tumors are related to the breast in only a regional sense.

HISTOLOGIC CLASSIFICATION OF CARCINOMAS OF THE BREAST

I. Paget's Disease of the Nipple
II. Carcinomas of Mammary Ducts
  (a) Noninfiltrating tumors
    1. Papillary carcinoma
    2. Comedocarcinoma

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*The authors are presenting this paper by request and as part of a symposium on mammary cancer. They are quite aware of the fact that it contains no new material and justify it solely through the feeling that it may lessen somewhat the confusion common to the classification of carcinomas of the breast. The classification presented, naturally, is that of the Memorial Hospital.

(b) Infiltrating tumors
1. Papillary carcinoma
2. Comedocarcinoma
3. Carcinoma with productive fibrosis
4. Medullary carcinoma
5. Colloid carcinoma

III. Carcinomas of Mammary Lobules
(a) Noninfiltrating
(b) Infiltrating

IV. Relatively Rare Carcinomas
1. So-called sweat gland carcinoma
2. Intracystic carcinoma
3. Spindle-cell carcinoma, "adenosarcoma"
4. Adenoid cystic carcinoma
5. Carcinoma with osseous and cartilaginous metaplasia
6. Squamous carcinoma
7. Malignant variant of fibroadenoma and cystosarcoma phyllodes

PAGET'S DISEASE OF THE NIPPLE

Paget's disease has long been recognized as a clinical and pathologic entity and as such does not require discussion. The lingering debate as to whether this is a disease primary in the epidermis of the nipple or whether it represents an outward extension of cancer cells from underlying mammary ducts cannot be settled here. Certainly in the ordinary case of Paget's disease of the nipple there is easily identifiable underlying carcinoma of mammary ducts (Figs. 1 and 2) having no structural peculiarities that would separate it from those duct carcinomas that are not accompanied by Paget's disease. Certainly there are those cases, the exceptional ones, where underlying involvement of mammary ducts is distinctly minimal, but we have never had an example where we could say that the underlying mammary ducts were free from involvement. To sustain fully the thesis of primary origin in the epidermis a case is needed in which the entire nipple was sectioned serially and shown to have mammary ducts entirely free from malignant alteration. From time to time random sections have been seen in which the process was limited to the epidermis. Invariably when further material from such a case was cut, involvement of underlying ducts was shown. If Paget's disease is primary in the epidermis it seems rather odd that the infiltrating tumor associated with Paget's disease of the nipple is always a tumor with the morphologic characteristics of carcinoma of the breast and that this structure is present in metastases. If Paget's disease of the nipple is primarily epidermal in origin, it is peculiar that the infiltrating tumor does not commonly assume the form of an epidermoid carcinoma in both the primary tumor and its metastases. Failure to do this puts considerable strain on the theory of origin in epidermis. Even when a lesion identifiable as Paget's disease of the nipple shows epidermoid structural traits, this is not proof of primary epidermal derivation since duct carcinomas of the breast may assume the properties of epidermoid carcinoma in both the primary tumor and node metastases in the absence of overlying Paget's disease of the nipple. To cite examples of extramammary Paget's disease does not necessarily solve the problem of this disease of the nipple. The impression has been gained that some cases of extramammary Paget's disease are not critically diagnosed. Where

the resemblance to Paget's disease of the nipple is satisfactory, it is necessary that evidence be presented that sweat gland ducts in the region were not involved. Extramammary Paget's disease is so uncommon that all of its histogenetic problems have not been settled. We have seen no case which showed critically the primary origin of Paget's disease in the epidermis of the nipple.

Fig. 1.

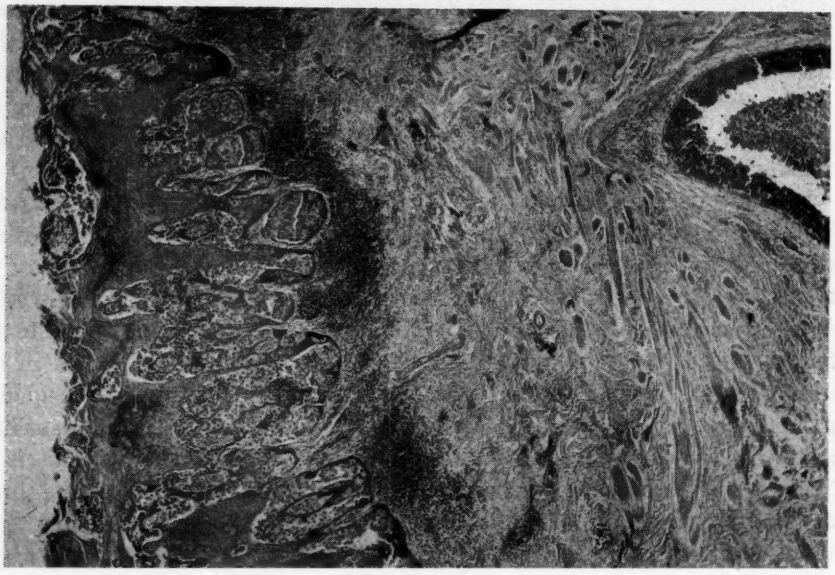


Fig. 2.

Fig. 1.—Paget's disease of the nipple; involvement of mouth of mammary ducts.
Fig. 2.—Paget's disease of the nipple; involvement of deeper lying duct.

The clinical implications of Paget's disease of the nipple are, for the vast majority of cases, quite clear-cut and they indicate the necessity for radical amputation of the breast. Even in Paget's disease of the nipple, in which there is no clinically palpable underlying lesion, one undertakes considerable responsibility when recommending any procedure short of radical mastectomy. Metastases have been found in Paget's disease when no definitive tumor was palpable. Sections from such cases have shown the presence of miniature infiltrating carcinoma.

CARCINOMA OF MAMMARY DUCTS

Noninfiltrating Tumors.—

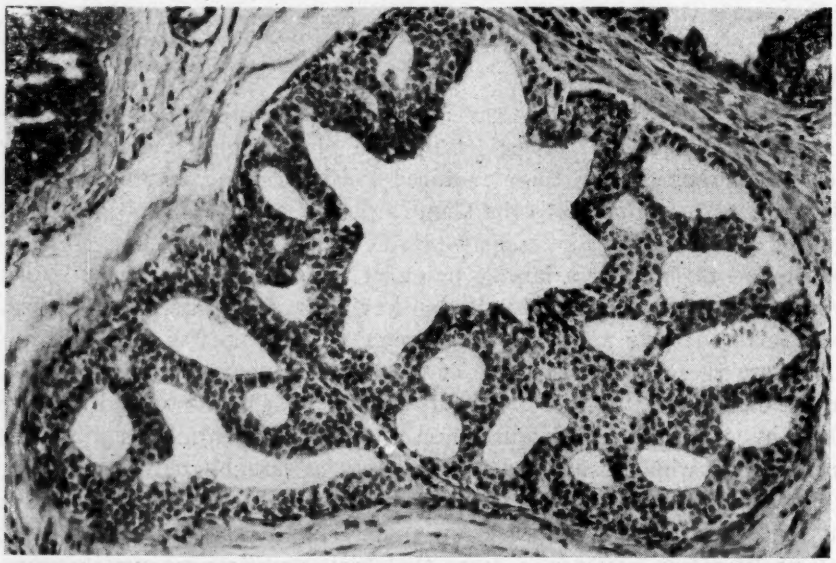
Papillary carcinoma: The term noninfiltrative papillary carcinoma designates a tumor of specific histologic type in a phase highly favorable for cure by means less radical than those required for infiltrating carcinomas. Structurally the disease is limited to the mammary duct system and either the large, medium-sized, or small radicles may be affected. Whereas there may be extensive spread throughout a large portion of the duct system, there is usually fairly well-defined segmental distribution having at least quadrant localization. In some cases one gets a distinct impression of multiple foci of origin and in the rare case there are apparently independent primary sources in different quadrants of the breast. Microscopically the tumor is characterized by atypical papillary hyperplasia of duct epithelium which is heaped up in solitary finger-like projections which usually do not possess a vascularized stalk (Fig. 3). Papillary anastomosing strands of tumor bridge the lumen of the duct leaving vacant spaces which result in a cartwheellike structural pattern. In some areas the cell proliferation becomes so dense that basic papillary properties are overgrown. The duct lumen is progressively reduced and finally obliterated. Characteristically, the central areas of intraductal tumor do not undergo necrosis as is the case in comedocarcinoma. Some of these tumors do not exhibit a high degree of cellular atypy. The individual cells are usually of medium size and do not vary a great deal in configuration and stainability. Hyperchromatism is not impressive and the rate of cell division is low. The histologic alteration of greatest significance is a disturbance in cell polarity. These various factors combine in quality and degree beyond that found in benign duct papillomatosis. It must be acknowledged that there is a zone of altered cell growth where the diagnosis of carcinoma versus atypical papillomatosis is a question of occult distinction and must be accepted or rejected on grounds of faith in the pathologist or lack of it. In some instances in which the presence of noninfiltrating papillary carcinoma is quite obvious, there will be additional outlying or adjacent foci in which the degree of structural change is distinctly less advanced and this leads one to believe that pre-existing papillomatosis had been present and had undergone malignant transformation.

In our material this is a rare variety of mammary carcinoma seen only two to three times per year, during which time about 500 surgical specimens of mammary carcinoma are examined in the laboratory. As a result of having seen a large number of referred patients in whom the diagnosis of noninfiltrating

papillary carcinoma has been made, we are convinced that it is made much too often. The vast majority of such referred diagnoses proved to be nothing more than benign duct papillomatosis. The error in diagnosis is hence most often made in the direction of unjustified diagnosis of carcinoma.

A preoperative, clinical diagnosis of carcinoma in these patients is unlikely since the secondary physical signs of breast carcinoma are not present

Fig. 3.



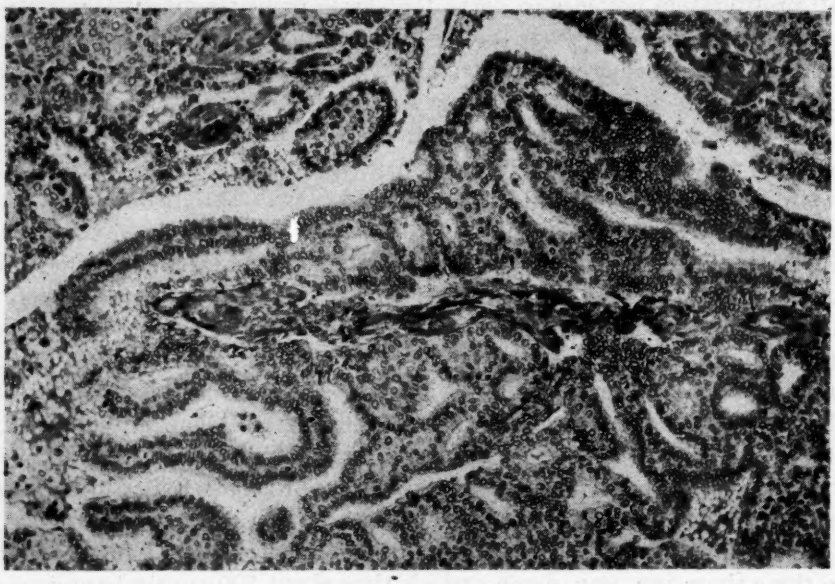


Fig. 4.

Fig. 3.—Noninfiltrating papillary carcinoma of ducts.
Fig. 4.—Infiltrating papillary carcinoma.

and the lesion is not often well demarcated and discrete. Bleeding nipple may or may not be present. For these reasons such cases are apt to come to the pathologist's attention at the time of operation when a locally excised portion of breast tissue is submitted for frozen section. In the gross, one sees multiple mammary ducts which appear partly or entirely filled with friable grayish-white tissue. The central, intraductal necroses of comedocarcinoma are not present. It is very difficult in some cases to be certain from frozen sections that there is no infiltration. Under these circumstances it is our policy to recommend simple mastectomy. If no infiltration is found after study of subsequent paraffin sections, further operative procedure is unnecessary. If, however, the tumor is shown to be infiltrating, it is obligatory that radical dissection be carried out. In no case of noninfiltrating papillary carcinoma is it safe to stop short of simple mastectomy since no one can guess accurately the distribution of the tumor within the breast.

Comedocarcinoma: The noninfiltrating form of comedocarcinoma differs from papillary carcinoma in that the growth within the ducts is generally more solid and is accompanied by central necrosis. On gross examination there is an expressible core of soft or semisolid, usually somewhat greasy, material. It is this property of simulating a comedone that is responsible for the descriptive term employed. Comedocarcinomas may arise in any portion of the duct system. If one plots the distribution of these tumors he will discover that, contrary to usual teaching, they more frequently begin in the smaller and intermediate duct divisions. The intraductal proliferation of cells often expands a small duct to and beyond the dimensions of the major mammary ducts. True enough the most classical and impressive cases do involve the larger channels but at the same time they are exceptional. Histologically the intraductal proliferation is decidedly atypical in a degree far exceeding that which is usual in papillary carcinoma. The cells concerned are usually larger, are more hyperchromatic, show greater loss of polarity, and in an overall sense are much more anaplastic (Fig. 5). In so far as the pathologist is concerned, these tumors present in part the same frozen section problem as noninfiltrating papillary carcinoma. They are not so difficult, however, from either the gross or the microscopic point of view.

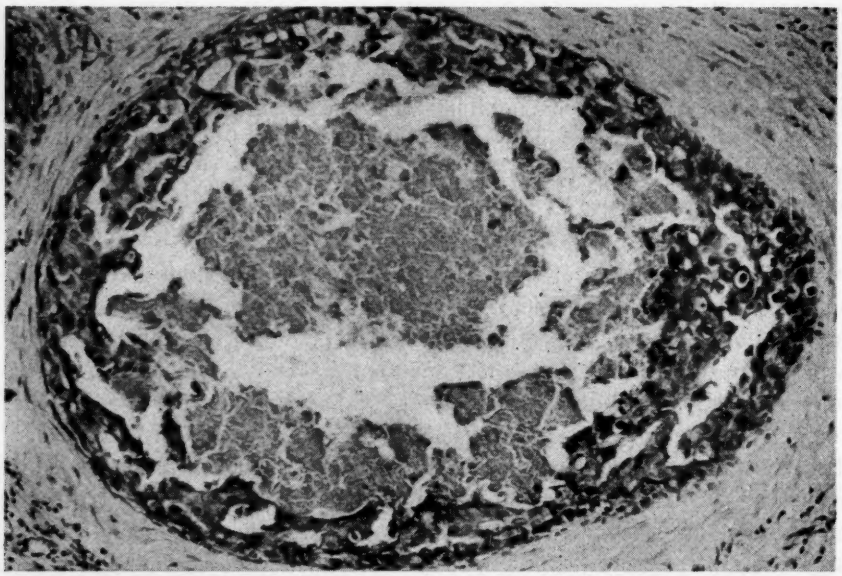
A true noninfiltrating comedocarcinoma is another rare type of mammary cancer constituting less than 1 per cent of all cases. The chief reason for specific mention of this tumor as an anatomic type is that it represents another example of breast carcinoma rationally treated by means of simple mastectomy.

Infiltrating Tumors.—

Infiltrating papillary carcinoma: Infiltrating papillary carcinoma of mammary ducts represents a later phase of the tumor described under papillary carcinoma. In the more advanced invasive stage, its papillary qualities are well maintained (Fig. 4). The tumor incites little or no reactive fibrosis in the breast and on section it appears cellular, soft, and friable. Considerable bulk is commonly attained and other attributes are circumscription without encapsulation and a tendency to irregular necrosis which is usually central. Skin attachment

is customarily very late in the course of the disease and seldom seen unless the tumor is very large. Rate of growth is slow and when there has been a history of recent rapid enlargement, this can nearly always be explained by finding large areas of anemic or hemorrhagic necrosis with edema and exudative reaction in and about the tumor. Important to mention is the ordinarily long de-

Fig. 5.



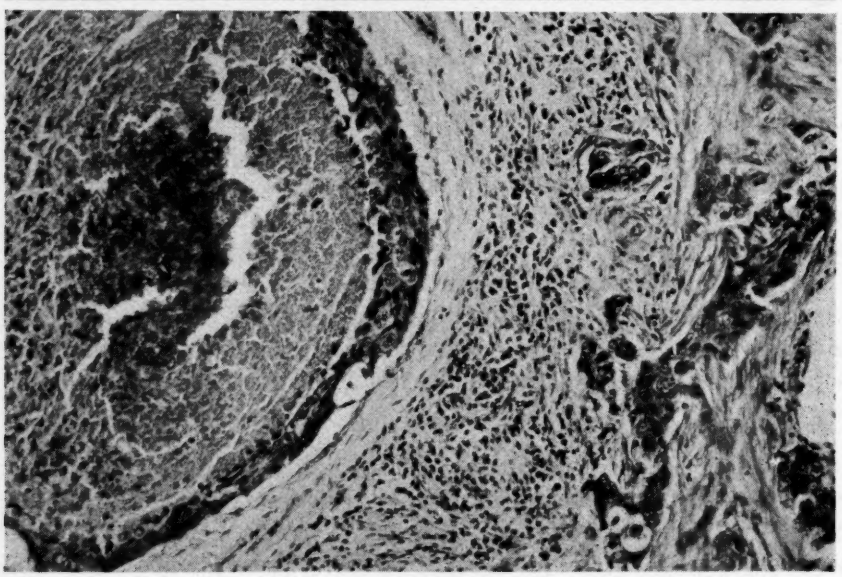


Fig. 6.

Fig. 5.—Noninfiltrating comedocarcinoma.
Fig. 6.—Infiltrating comedocarcinoma.

lay before axillary node involvement takes place. In the breast tissue itself the tumor shows little ability for intramammary spread along periductal or other lymphatic channels.

Due to aforementioned low-grade infiltrative qualities, these tumors are easily movable on palpation of the breast. This factor, combined with a lack of firmness, has in a number of instances led to a clinical diagnosis of fibroadenoma. The practice of aspiration biopsy at Memorial Hospital obviates any delay in correct diagnosis. In those cases in which local excision is done the gross aspect or, if needed, frozen section will disclose the true nature of the tumor and the radical operation can then be carried out. Conservatism is unwarranted in spite of the better prognostic outlook.

Infiltrating comedocarcinoma: Comedocarcinoma is almost invariably infiltrative when its presence is discovered. The only feature distinguishing it from other forms of infiltrating duct carcinoma is the accented feature of intraductal growth (Fig. 6) which is manifest both grossly and microscopically. If the disease is very advanced little of the quality of intraductal growth is retained and, as a consequence, such tumors lack much of the distinctiveness of classical comedocarcinomas. There is every range of balance between the properties of intraductal growth and those of infiltration. Naturally where infiltration is minimal the prognosis is correspondingly more favorable.

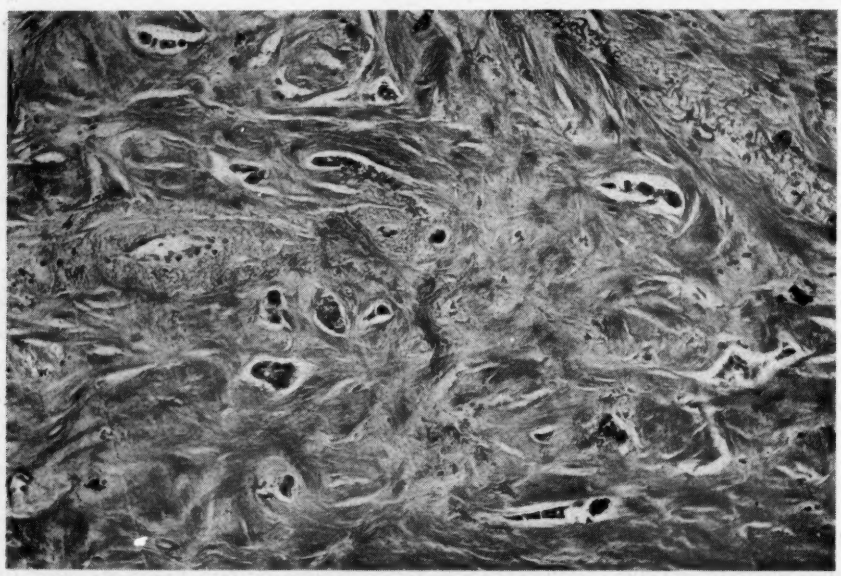
The histologic characters of infiltrating comedocarcinoma are very varied and from case to case one encounters tumors that grow after the fashion of ordinary scirrhous carcinoma or medullary carcinoma, or perhaps the tumor becomes largely colloid. Occasionally the cytology corresponds to that of so-called apocrine sweat gland carcinoma and again certain areas of an infiltrating comedocarcinoma become spindle cell or otherwise pleomorphic in make-up. In other words the infiltrating forms of comedocarcinoma have all the histologic potentialities of the various forms of duct carcinoma next to be described.

Infiltrating duct carcinoma with productive fibrosis: Tumors comprising the group of carcinomas with productive fibrosis are far and away the commonest forms of mammary cancer, aggregating roughly 70 per cent. Included here are the tumors that may be summed up as "ordinary mammary scirrhus." We are broadening this interpretation, however, to include some more cellular varieties in which the growth is less scirrhous. Even those cellular tumors referred to as carcinoma simplex show more or less desmoplasia or productive fibrosis, and to include in a classification scheme a separate heading for every microscopic variant creates added complication—an end already rather capably achieved in the foregoing classification.

For extreme forms of scirrhous carcinoma the term fibrocarcinoma has sometimes been used. For the more cellular form of this type one may employ the descriptive term carcinoma simplex. As would be expected, the majority of tumors falling in this large group lie between these extremes. Correspondingly, the degree of structural distortion seen in the histologic growth patterns is widely variable. Certain members of this group are quite orderly and grow

in single strands, smaller or larger sheets, and form lumina with varying frequency. The individual cells are usually medium sized and relatively uniform in their size, shape, and staining qualities. Every transition from this more or less orderly type of growth to more cellular hyperchromatic pleomorphic carcinoma is encountered (Figs. 7, 8, 9, and 10). At the other extreme are

Fig. 7.



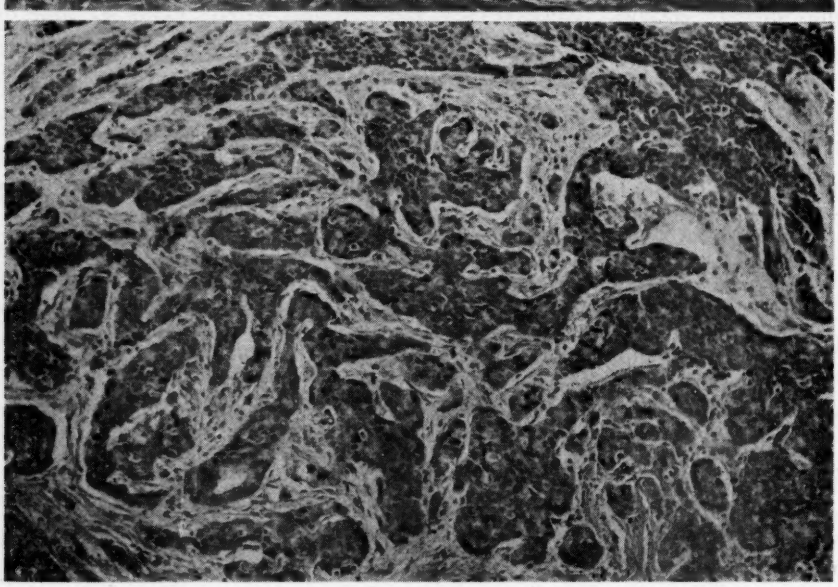
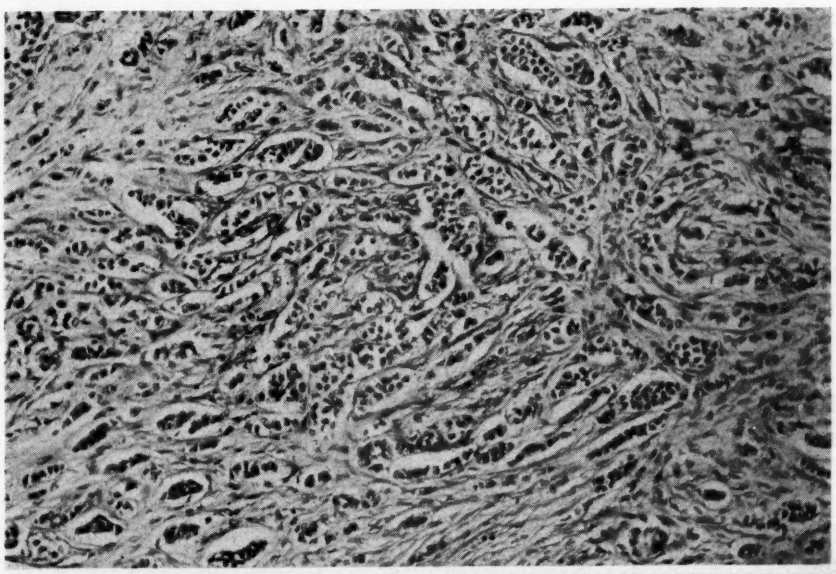


Fig. 8.

Fig. 7.—Infiltrating duct carcinoma with productive fibrosis.
Fig. 8.—Infiltrating duct carcinoma with productive fibrosis.

examples of almost acellular tumors in which the cells are so sparse that diagnosis of cancer in a limited field might be difficult. In such highly fibrotic tumors the infiltrating epithelial cells are sometimes so densely compressed between collagen fibers that they become narrow and spindle in contour in such a way that they simulate connective tissue cells.

Fig. 9.



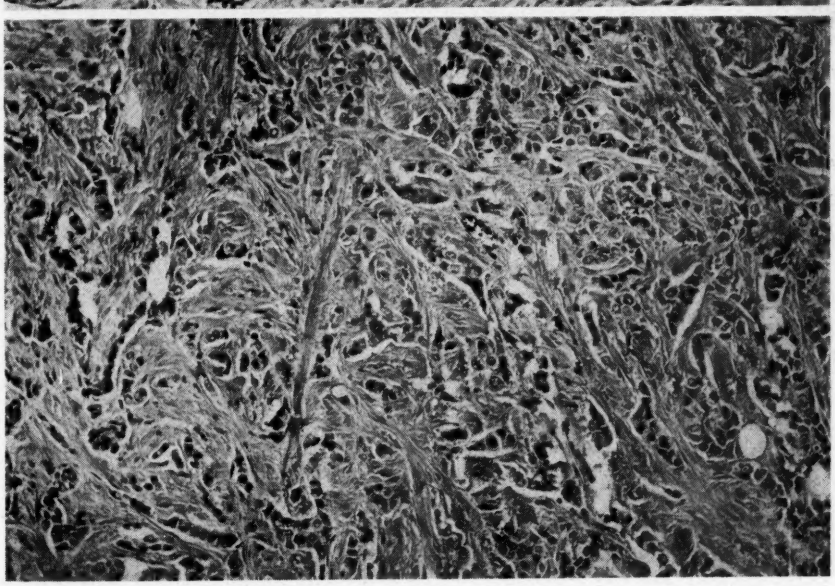


Fig. 10.

Fig. 9.—Infiltrating duct carcinoma with productive fibrosis.
Fig. 10.—Infiltrating duct carcinoma with productive fibrosis.

The macroscopic characteristics of these tumors are easily recognized and these are the forms of mammary carcinoma usually described when the classical gross traits of mammary carcinoma are enumerated. The majority of these tumors are not rounded but are discoid and have distinctly irregular edges which radiate from the general periphery of the tumor into adjacent fibrous or fatty breast tissue. An outstanding attribute is firm and almost unyielding induration. Under the knife they cut with increased resistance and the exposed surface is depressed below the level of the surrounding breast tissue. The cut surface of the tumor exhibits the prosaic yet authentic striate, yellowish, chalky streaks, scattered over a generally grayish or pale grayish-yellow background. Spontaneous hemorrhage and large areas of necrosis are much less common in this type of mammary carcinoma than in many others. On the average these tumors are 2 to 3 cm. in greatest diameter. Great bulk is somewhat exceptional.

Radical mastectomy is the only approved surgical procedure for tumors in this infiltrating group. This applies even to those tumors that are designated numerically as of low-grade malignancy. Whereas the frequency with which the axilla is involved in these tumors of lower grade of malignancy is distinctly less than the more histologically malignant, it is too frequent to justify the risk of limited breast surgery.

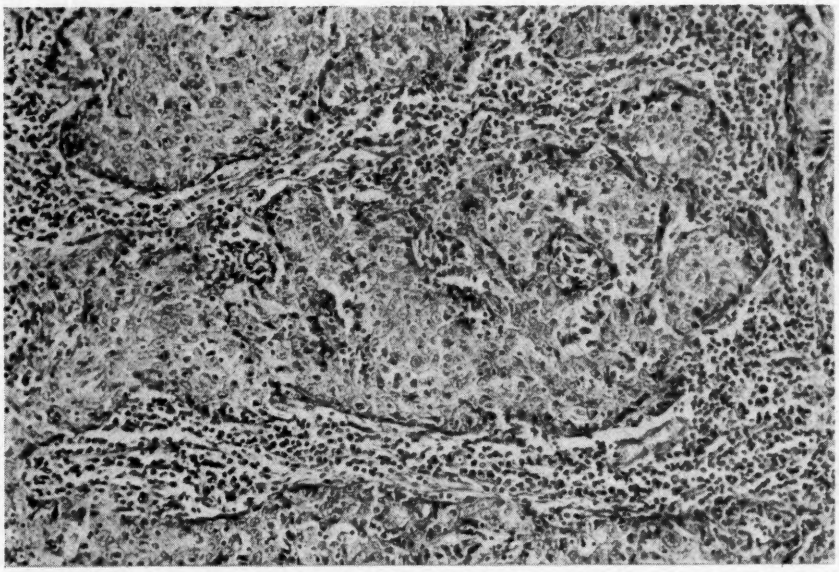
Medullary carcinoma: Medullary carcinoma is characteristically composed of large, oval, rounded or polygonal cells with abundant basophilic cytoplasm and large vesicular nuclei. The cells are put together usually in rather broad, anastomosing, medullary or plexiform masses. In some of the tumors there is fairly well-developed papillary quality and in such areas the formation of lumina is not unexpected. In still other examples the growth pattern is highly indifferent and almost syncytial in its diffuseness. The degree of hyperchromatism, nuclear variation, and cytoplasmic variation as to size and shape is not great. Hemorrhagic or anemic necrosis is common. The tumors are apt to be quite rich in mitoses.

A great many medullary carcinomas are accompanied by abundant infiltrations of small lymphocytes to such an extent that they seem to be a formal component (Fig. 11) in the make-up of the tumor. Their presence cannot be explained as a reaction to broken down tumor since they may be seen in very small tumors that do not have foci of necrosis. They arouse the speculation that they are a manifestation of host reaction to the presence of tumor. This structural peculiarity is sufficient to justify specific recognition and to report such tumors as medullary carcinoma with lymphoid infiltrate.

Grossly, medullary carcinomas have highly distinguishing qualities and they stand in contrast to the group described in the preceding section. They are commonly quite bulky, measuring 4, 5 and 6 cm. in diameter, and now and then these dimensions are doubled. They are rounded or globoid, cut with little resistance, and although not encapsulated these tumors are distinctly circumscribed and present a smooth periphery. On cut section the exposed surface bulges above the level of the surrounding tissue, the tumor is soft, and chalky streaks are unexpected. Where the cancer is fully viable it is grayish-white,

but as a group these tumors are quite prone to spontaneous hemorrhage and necrosis and for this reason may present variegated coloring. Size for size they are distinctly less infiltrating than scirrhous carcinomas as judged by the local infiltration in the breast as well as the frequency of axillary node metastases. Due to relatively low-grade infiltrative tendencies and the habit of circumscription, they are apt to show clinically little or no skin attachment or dimpling.

Fig. 11.



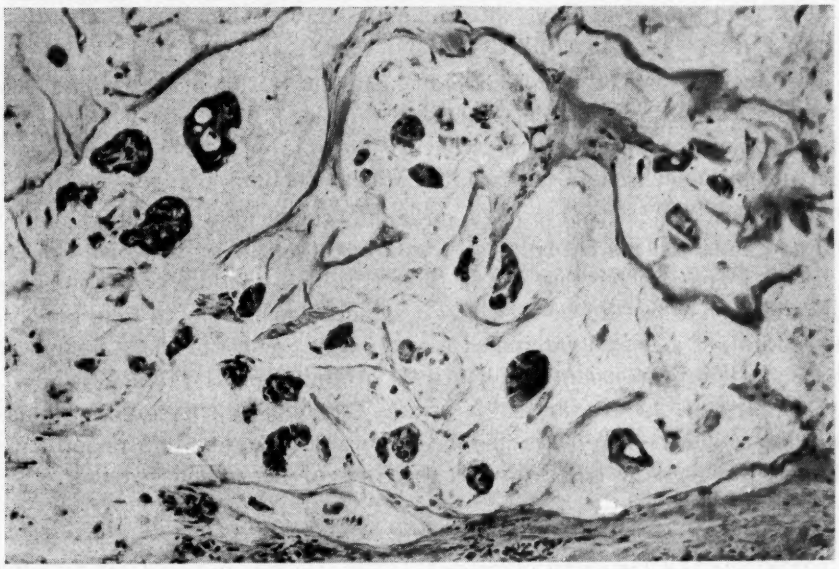


Fig. 12.

Fig. 11.—Medullary carcinoma with lymphoid infiltrate.
Fig. 12.—Colloid carcinoma of breast.

As a rule the axillary nodes do not contain tumor unless unless the primary is as large as 1.5 to 2 cm. and tumors may reach very large size or even fungate without having metastasized to the axilla. They constitute about 15 to 20 per cent of breast carcinomas.

In surgical control of this disease, radical mastectomy is again the only procedure that can be properly advised. Even though these tumors have seldom produced axillary metastases when 1½ cm. or smaller in diameter, this does not constitute any assurance for a particular case and any conservative procedure involves increased risk to the patient.

Colloid carcinoma: The diagnosis of colloid carcinoma of the breast is necessarily imperfect in many cases, inasmuch as it represents the employment of a descriptive term for a histologic alteration which is present from case to case in varying degrees of completeness (Fig. 12). When to use the term and when not to use it is a more or less arbitrary matter which will differ from person to person. Where a laboratory is handling a bulky material there is apt to be little inclination to employ this term unless the gelatinous character of the tumor is highly developed. On the other hand, if a limited amount of pathologic material from breasts is available this term is likely to be much more readily applied because of the natural human instinct to dress up material as gaily as possible. Particularly in some rather bulky mammary cancers there is a tendency toward colloid change. On the other hand, a carcinoma of the breast is occasionally encountered as small as 1 cm. or less in size in which the whole body of the tumor is soft and gelatinous with no firm noncolloid portion. Our own practice is to employ the term colloid carcinoma when this is an obvious character seen in the gross. When the colloid aspect of the tumor is a random microscopic finding, we are inclined to designate the tumor as an infiltrating duct carcinoma, partly colloid.

We have not as yet noted colloid change in a tumor which had characteristics indicating origin from mammary lobules. This is not necessarily a permanent point of view since it is hardly possible to predict in any group of malignant epithelial tumors the inability to show colloid change.

Sometimes one is hard put to designate the degree of malignancy in a colloid carcinoma. This is principally true in those tumors in which the cancer cells are very sparse. All that can be done is to base the idea of the malignancy of the tumor on what can be seen but it is not a good plan to take one's ideas of the grading of a colloid carcinoma too seriously. Some of those tumors which are both small in dimension and relatively acellular will be found to have produced axillary metastases, and it is unwise to trifle with colloid carcinoma no matter how sluggish it appears under the microscope. Grading in most colloid carcinomas can best be based on the structure of noncolloid portions.

CARCINOMAS OF MAMMARY LOBULES

Noninfiltrating Lobular Carcinoma.—In a previous publication[2] we referred to noninfiltrating lobular carcinoma as "lobular mammary carcinoma in situ." This form of mammary carcinoma usually goes unrecognized. In all probability

this is largely caused by its extremely low rate of occurrence. Perhaps, because of lack of material or interest in the structural attributes of mammary lobules, pathologists have spent little effort in their study. Evidence in this direction is furnished in the recently published cumulative index of the *American Journal of Pathology* covering a twenty-year period from 1925 through 1944. Included are only twelve articles on human breast pathology and but one of these is primarily concerned with the mammary lobules.

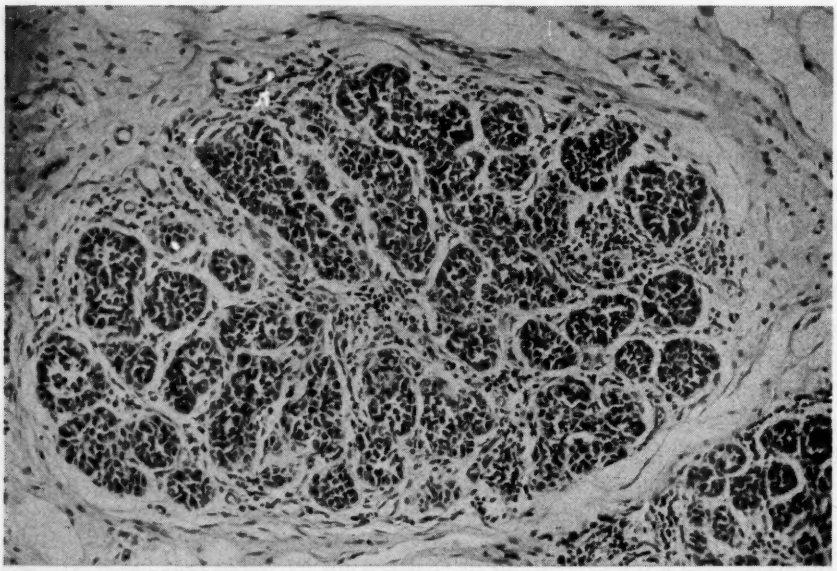
Microscopically, one finds in limited and sometimes large areas numbers of mammary lobules, some of which are decidedly larger than normal and whose cellular make-up is greatly changed (Fig. 13). The cells within the acinar components, although not large, exceed the size of normal acinar cells. They pile up in a loose or compact fashion with no orderly layering. Almost always the acinar lumina are obliterated and the cells within lack coherent arrangement. They differ little in size but assume various shapes tending to be round or ovoid where there is least cell crowding. The nuclei are not hyperchromatic and may actually appear pale, somewhat after the manner of the cells in Paget's disease of the nipple. Mitoses are few. The cytoplasm is moderately opaque and does not have outspoken eosinophilic or basophilic quality. The involvement of a single lobule may be complete or partial, and in the latter instance nice contrast is demonstrated. In making the diagnosis microscopically of lobular carcinoma in situ, one must not confuse the intralobular extensions of tumors which are of duct origin. Such extensions are only superficially confusing with true lobular carcinoma in situ.

Lobular mammary carcinoma in situ cannot be diagnosed clinically nor can a diagnosis be made on gross pathologic examination. All that one sees in the gross are groups of rather large lobules which may be more or less closely spaced and concentrated within a relatively limited area. For this reason, this form of noninfiltrating carcinoma represents an incidental finding in local excisions which have been done for presumably benign conditions. The only physical sign elicited where this lesion exists is ill-defined induration and this only in the exceptionally well-developed case. In our opinion, simple mastectomy should be done when the diagnosis of lobular carcinoma in situ is made and if, in subsequent pathologic material, infiltration is discovered, further surgical procedure is necessary.

Infiltrating lobular carcinoma: Infiltrating lobular tumors make up about 3 to 5 per cent of all breast carcinomas. As a histologic entity they are not widely recognized. The microscopic structural pattern assumed by these tumors is, however, quite characteristic once its peculiarities are appreciated. To be certain of the identity of this infiltrating form of cancer as one arising in lobules requires the observation of a large mass of breast material sufficient to supply enough key cases which show transitions from the noninfiltrating form of the disease to the fully infiltrating tumor. The infiltrating portions of lobular carcinomas typically reveal threadlike strands of tumor cells rather loosely dispersed throughout a fibrous matrix. After infiltration has occurred there is

no tendency for the cells to simulate atypical lobules. Sheetlike growth is distinctly uncharacteristic. The individual cells are small or medium-sized and commonly elliptical or spindle-shaped due to the denseness of the surrounding fibrous tissue matrix (Figs. 15 and 16). They are rather uniform in their staining properties and exhibit relatively little cytologic irregularity. The structure of the tumor in metastases is apt to contrast considerably with the

Fig. 13.



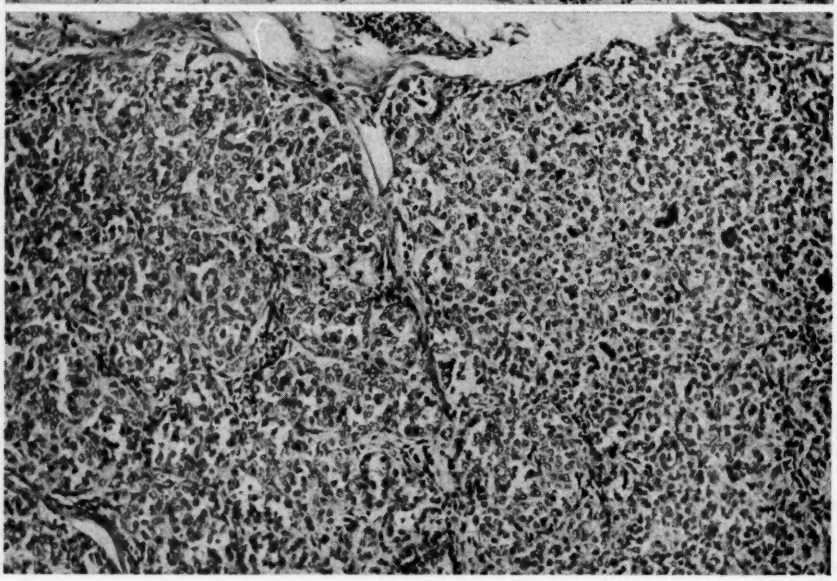


Fig. 14.

Fig. 13.—Noninfiltrating lobular carcinoma (lobular carcinoma in situ).
Fig. 14.—Early infiltrative phase of lobular carcinoma.

commonly rather acellular structure of the primary tumor. In extreme examples the axillary metastases actually simulate lymphosarcoma. We have seen several referred patients in whom the pathologic diagnosis of lymphosarcoma had been made from sections of axillary nodes which contained metastases from undisclosed breast primaries. Great cellularity in the primary tumor is unusual but there are occasional cases in which this does occur.

Fig. 15.

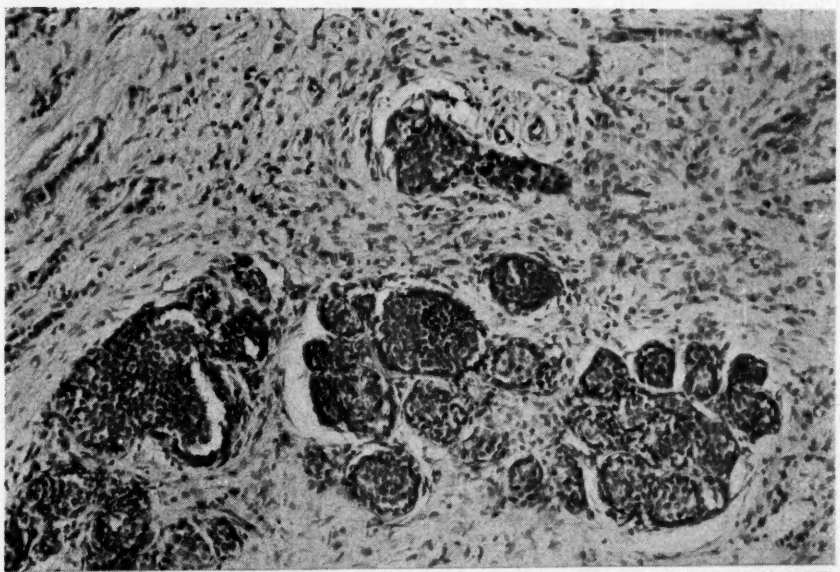


Fig. 16.

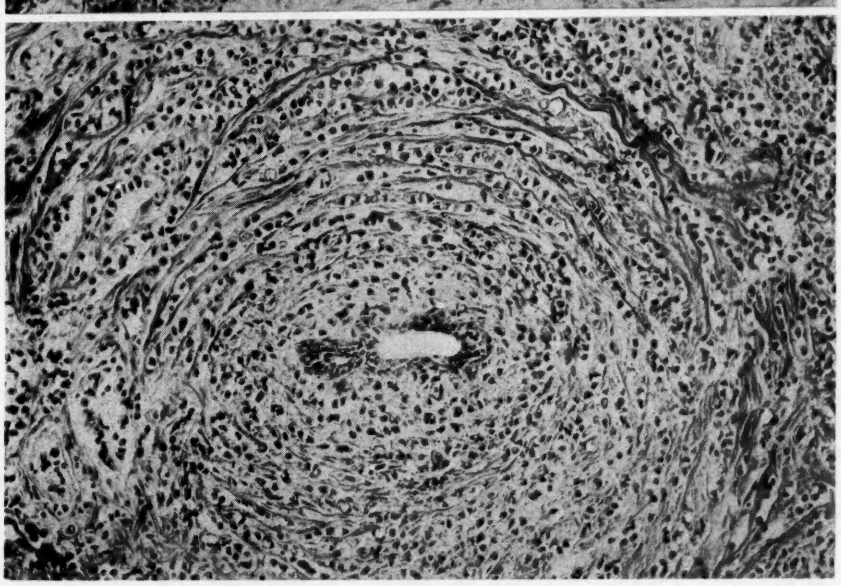


Fig. 15.—Noninfiltrating and infiltrating lobular carcinoma.
Fig. 16.—Periductal infiltration pattern likely to be assumed by lobular carcinoma.

In the gross, infiltrating lobular carcinomas are more apt to resemble scirrhous carcinomas than other gross anatomic types. The tumors, as a rule, are discoid or somewhat irregular in shape and rather poorly demarcated. They are tough and firm and are less apt to show chalky streaks so common in ordinary mammary scirrhus. On some occasions the gross specimen can be quite confusing and misleading. These episodes usually come about at the time of operation when a locally excised specimen of breast tissue is sent in for frozen section diagnosis. Such a specimen may present no distinctly visible lesion and yet contain a palpable area of peculiar induration, the precise limits of which are vague. Such lesions can cause difficulty in frozen section diagnosis, since the cell proliferations are in minute or single-cell strands or composed of isolated single-cell units. After the diagnosis of cancer is made it is well to be prepared for querulousness from the operating surgeon who understandably would like to be operating for something more finite than indistinct induration.

These tumors are fully aggressive mammary cancers and as such call for radical surgical measures.

RELATIVELY RARE CARCINOMAS

So-called Sweat Gland Carcinoma.—It should be understood here that sweat gland carcinoma is not carcinoma of the sweat gland appendages of the skin of the breast. The term sweat gland carcinoma needs further qualification and is more properly referred to as apocrine sweat gland carcinoma since the cell type concerned has real resemblance to the cells of cutaneous apocrine sweat glands. These tumors constitute about 1 per cent of mammary carcinomas and are a specific histologic type characterized by large eosinophilic cells which are oftentimes columnar and contain abundant eosinophilic cytoplasm and relatively small nuclei (Fig. 17). All of these qualities, with the exception of the eosinophilic quality of the cytoplasm, are subject to considerable variation. In tumors where this characteristic does not exist the diagnosis is not justified.

In the classification given, so-called sweat gland carcinoma has not been listed under a specific anatomic site of origin such as duct or lobule. Avoiding this was purposeful. The cells making up these tumors bear considerable resemblance to cells found in both the ducts and lobules of the breast which have undergone apocrine metaplasia. In the material that we have available which gave evidence for a site of origin, the mammary ducts were implicated. In the unusual but most satisfactory case, highly convincing transitions are seen ranging from typical apocrine epithelium to apocrine epithelium in atypical hyperplasia to intraductal apocrine sweat gland carcinoma and finally to infiltrating carcinoma made up of apocrine-like cells. Since, however, apocrine metaplasia commonly affects the lobular epithelium, it does not seem justifiable to exclude the lobules as a potential source of origin.

There are no unique characters that make it possible to identify these tumors grossly. Customarily they resemble the more cellular infiltrating duct carcinomas with more or less productive fibrosis. Extreme degrees of fibrosis are not usual. Occasionally the gross appearance is that of a comedocarcinoma.

The morphologic specificity of these tumors is evident only microscopically. The therapeutic implications of infiltrating mammary carcinomas apply here. If perchance a noninfiltrating form is encountered, simple mastectomy should suffice.

Intracystic Carcinoma.—It is distinctly infrequent to see an unequivocal anatomic example of this type of mammary carcinoma. That this should be a

Fig. 17.

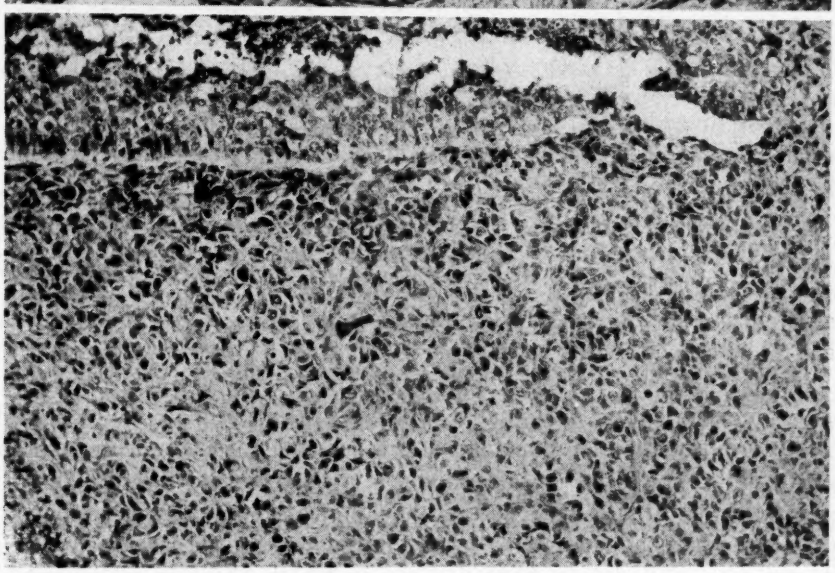


Fig. 18.

Fig. 17.—So-called apocrine sweat gland carcinoma of breast.
Fig. 18.—Duct carcinoma with spindle and polyhedral cells.

rare form is not surprising, inasmuch as the vast majority of cysts in the breast lose their epithelial lining when they become a few millimeters or more in diameter. Even in those cysts of the breast which still retain epithelial lining, atypical hyperplastic epithelial changes are nearly nonexistent. Intracystic papillomas are themselves very few in number if one includes only authentic examples of this lesion and excludes the common intraductal papilloma. The latter lesion is oftentimes loosely referred to as an intracystic papilloma, which it, indeed, is not. Sometimes in a true intracystic carcinoma there is residual noncancerous papilloma but these traceable lesions are almost a curiosity. This anatomic type has purposely been excluded from listing under either the tumors of duct or lobule origin since by the time that an intracystic carcinoma has developed, its exact point of origin is no longer demonstrable. It is difficult enough to decide where 1 and 2 mm. sized cysts arose. This tumor is more distinctly a gross than a microscopic entity.

In this numerically small group of mammary tumors, now and then a noninfiltrating tumor is discovered confined to the wall of the cyst. Usually infiltration is present and it is more apt to be advanced than limited. Even where there is considerable bulk of solid infiltrating tumor, at least a portion of the cyst is uninvolved in the malignant process. The intracystic portions of the tumor are nearly always partly papillary but they may be almost entirely solid and very cellular. The infiltrating portions assume a wide variety of structural patterns varying from highly cellular tumors to those that are predominantly scirrhous in character. We have never seen an infiltrating intracystic carcinoma which assumed any growth trait not common to one of the several forms of definitely established duct carcinoma. In no case has the intracystic carcinoma partaken of the histologic qualities seen in lobular carcinoma.

The disease is a rare one and hence opportunities to employ different forms of surgical procedure will be correspondingly few. In the rare case where one can be convinced of lack of infiltration, simple mastectomy as opposed to radical mastectomy is the reasonable form of treatment, but with infiltration there are all the implications of cancer of the breast in the ordinary sense.

Spindle-cell Carcinoma, "Adenosarcoma."—To the preceding terms carcinosarcoma may be added. Usage of these terms is not uniform. It is our practice to use such terms as adenosarcoma and carcinosarcoma as little as possible. They can of course be used in either a descriptive or a derivative sense. In the first instance, one would signify a malignant epithelial tumor having areas which simulate a malignant connective tissue tumor. When used in a derivative sense, that is, a histogenetic sense, the terms indicate a malignant tumor containing cells of both epithelial and mesodermal origin. In so far as the breast is concerned, it appears probable that the only tumor properly meriting a diagnosis of adenosarcoma or carcinosarcoma is the malignant variant of cystosarcoma phyllodes or fibroadenoma in which there is malignant change involving both epithelial and connective tissue cells. No definite rules have been established as to the usage of such terms and when one employs them in manu-

script, explanation of usage is imperative to avoid confusion. In this classification these terms are used in a purely descriptive sense.

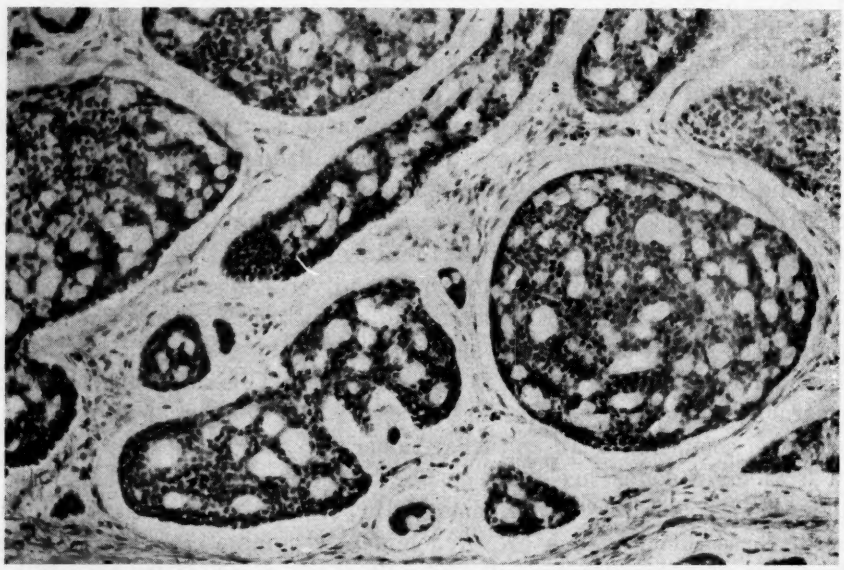
Spindle-cell carcinoma of the breast is so uncommon that only once in several hundred cases is it necessary to make the diagnosis. Thus the problem of terminology is a trifling one. Whether or not one is justified ever in making a diagnosis of spindle-cell carcinoma, unless there is at least some traceable gland forming or other epithelial quality, is a debatable matter among pathologists. Here again one deals in attitudes and is hard put to defend satisfactorily that attitude which has been assumed. A doctor is apt to be friendly or unfriendly toward the diagnosis of spindle-cell carcinoma in about that degree to which he accedes to the metaplastic capabilities of neoplasia in general and it is also dependent upon how broad a mass of neoplastic disease he has had to study. In making the diagnosis of spindle-cell carcinoma in the absence of definitely demonstrable epithelial structure, it is perhaps preferable to acknowledge some doubt as to the ultimate accuracy of the diagnosis. In this way one can avoid a certain amount of unnecessary argument and yet maintain his private opinion. Painstaking study of multiple blocks will oftentimes turn up the desired indisputable epithelial areas. It is also noteworthy that these tumors metastasize to regional lymph nodes, which is not the expected behavior in sarcoma. As a general rule applicable to neoplasms as a whole, it may be stated that it is much more common for an epithelial tumor to show pseudosarcomatous areas than it is for a connective tissue tumor to show pseudoepithelial areas. We have spoken of spindle-cell carcinoma in this section but it must be added that some of those tumors which are predominantly spindle cell show, in addition to this type of cell, a great variety of cells of all sizes and shapes which grow in a more or less indiscriminate pattern (Fig. 18).

These pleomorphic mammary tumors which have epithelial and pseudosarcomatous properties are quite apt to be bulky. Other factors associated with them are long duration and secondary ulceration of overlying skin. In an occasional case in which there are biopsies from succeeding local recurrences, it is sometimes observed that the recurrences at one time partake largely of epithelial quality, while at other times the pseudosarcomatous pattern is predominant. To our minds these observations reinforce the fundamental view that the tumors are primarily epithelial in origin. An exception has already been cited.

Adenoid Cystic Carcinoma.—This is a vanishingly rare breast carcinoma. Structurally it is absolutely indistinguishable (Fig. 19) from the adenoid cystic carcinoma of major and minor salivary glands as well as from mucous glands of trachea and bronchi. The same histologic type of tumor is also seen very occasionally arising from cutaneous sweat glands. We have seen only three examples of this tumor primary in breast. In one of these the adenoid cystic areas blended with areas growing like ordinary duct carcinoma with productive fibrosis. In addition there were ducts showing atypical papillomatosis and intraductal carcinoma. These findings suggest that the adenoid cystic carcinoma is another histologic variety of duct cancer.

The available inventory of these tumors is so small that a comprehensive account of their clinical behavior is not available. In other locations they are well known to have the ability to metastasize even though the clinical course may be prolonged. Until evidence to the contrary is presented, radical operation should be carried out.

Fig. 19.



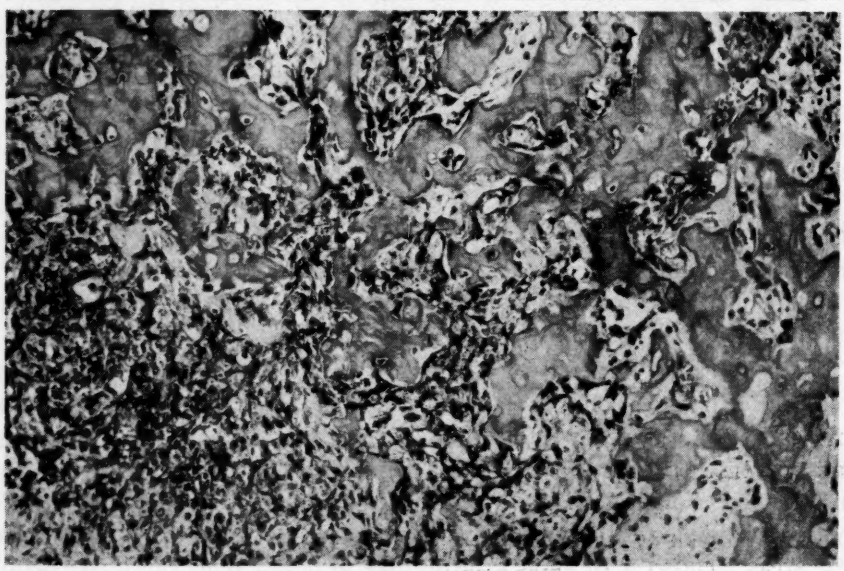


Fig. 20.

Fig. 19.—Adenoid cystic carcinoma of breast.
Fig. 20.—Mammary carcinoma with osseous metaplasia.

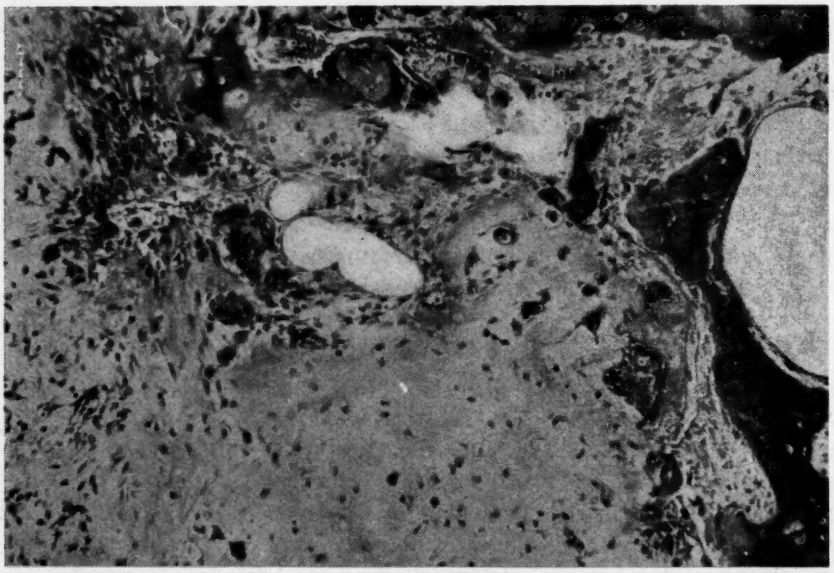
Mammary Carcinoma With Osseous and Cartilaginous Metaplasia.—This rare group of mammary carcinomas furnishes some of the most structurally bizarre breast tumors. The aforementioned metaplastic characters may be seen in only very limited areas of a tumor growing as infiltrating duct carcinoma or they may dominate the histologic picture almost to the exclusion of other elements. Not a few of these tumors show areas growing as squamous carcinoma. Invariably there is more or less spindle-cell component which can in most cases be traced in transitional stages to malignant epithelial cells. Actually it seems that spindle-cell metaplasia is an intermediate stage preliminary to the assumption of the osseous and cartilaginous qualities (Figs. 20 and 21). In some cases the cartilaginous areas predominate over the osseous and sometimes the reverse is true. Transition zones are not difficult to find. Although calcific bone trabeculae do occur, it is more common that the "osseous" component resembles osteoid tissue. Cytologically the osseous and cartilaginous areas appear malignant. This is apt to prompt the diagnosis of osteogenic sarcoma of the breast. We do not deny the possible existence of a mesodermal tumor of the breast having a structure consistent with osteogenic sarcoma since soft part sarcomas having these characters are well known to exist in other locations. It is felt, however, that the vast majority of breast cancers with such structure are examples of extraordinary metaplasia in fundamentally epithelial tumors. If, in a given case, no traceable transitions from epithelium can be detected, this thesis cannot be supported in a convincing manner. Having seen a considerable number of cases in this category, the impression has been gained that pathologists are so struck by the exotic aspect presented that no great search for histogenetic phases is made. It is a bit more sensational to send forth a diagnosis of osteogenic sarcoma of the breast than one of mammary carcinoma with osseous and cartilaginous metaplasia. The former has a motif of pleasurable astonishment while the latter is only prosaic.

The therapeutic principles applicable to all infiltrating mammary carcinomas are repeated here.

Squamous Carcinoma.—Reference is made to a tumor of the breast proper and not to squamous carcinoma of overlying skin. It might be preferable to list this tumor as infiltrating duct carcinoma with squamous metaplasia since the fuller term is descriptive of its source of origin. Limited and unimpressive areas of a few mammary duct cancers show the traits of squamous carcinoma but usually they are imperfectly developed (Figs. 22 and 23). Cases in which the structure of squamous carcinoma predominates and those which show keratohyaline granules, intercellular bridges, and epithelial pearls are a great rarity, too few to express practically in terms of per cent. Use of the term squamous carcinoma may be thought proper when there is a major degree of this sort of structure or when this is the sole structural form seen. As a compromise it is suggested that diagnosis in this group be recorded as infiltrating duct carcinoma growing partly (or largely) as squamous carcinoma. No case has come to our attention of a primary tumor of this sort that was purely squamous. Invariably there have been areas showing transition from duct carcinoma of not unusual

sort. Once in a great while, in a series of local recurrences, the structure in a biopsy may be solely that of squamous carcinoma. This structural change has never been traced in lobular carcinomas but it cannot be excluded as a theoretic possibility since acanthosis is a common variant in a great many carcinomas in widely divergent locations. On theory one may speculate on the possible existence of noninfiltrating squamous carcinoma of the breast.

Fig. 21.



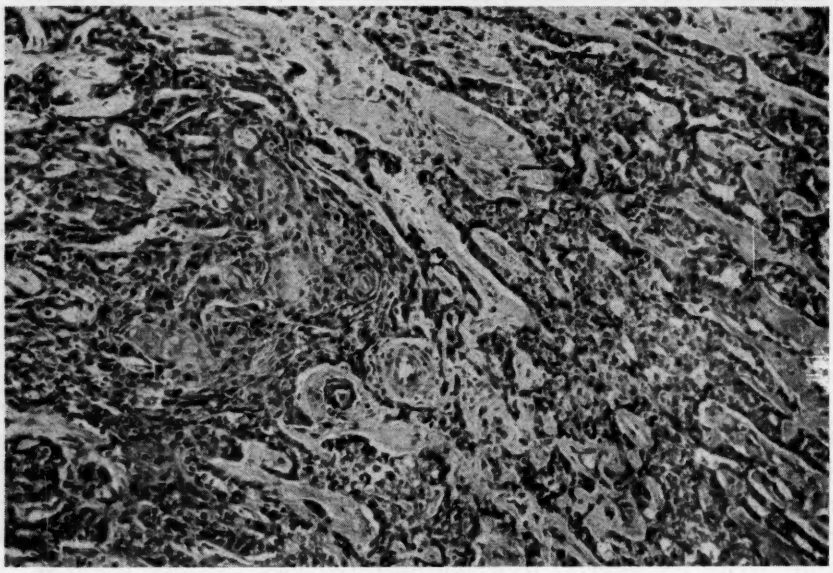


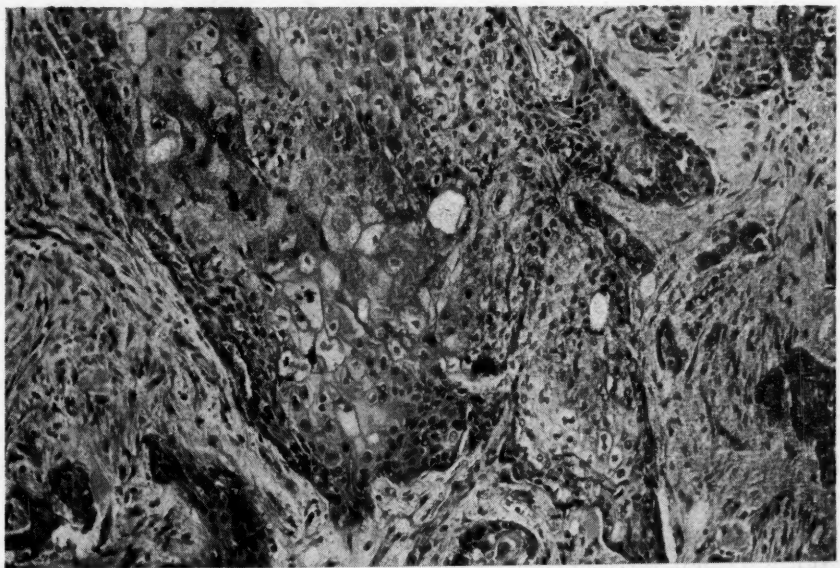
Fig. 22.

Fig. 21.—Mammary carcinoma with cartilaginous and osseous metaplasia.
Fig. 22.—Infiltrating duct carcinoma growing partly as epidermoid carcinoma.

No specific gross features typify this histologic type of tumor, but as a general rule they are relatively large.

Malignant Variant of Fibroadenoma and Cystosarcoma Phyllodes.—The frequency of these tumors is such that they are practically museum curiosities. The differences between intracanalicular fibroadenoma and cystosarcoma

Fig. 23.



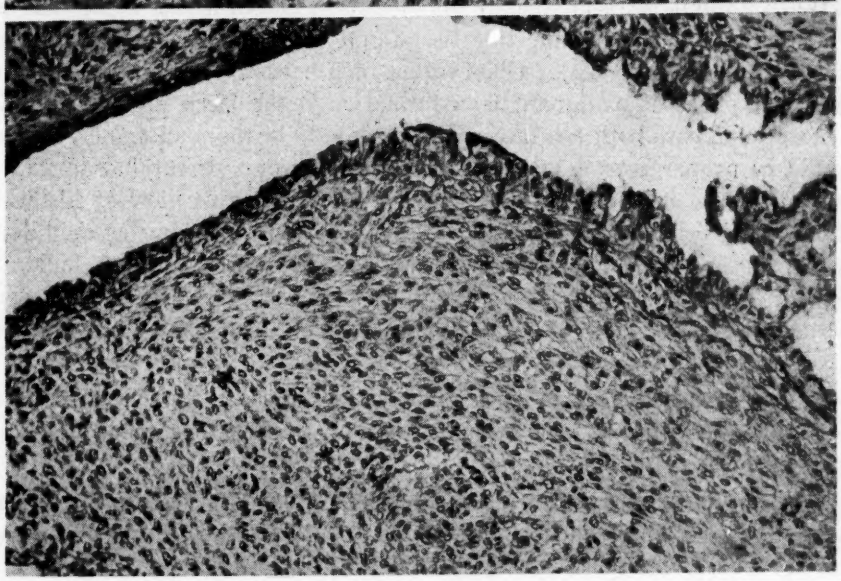


Fig. 24.

Fig. 23.—Mammary carcinoma which has assumed properties of squamous carcinoma.
Fig. 24.—Malignant phase of cystosarcoma phyllodes; death with lung metastases.

phyllodes are principally those of size—the size of the tumors as a whole as well as the size of the individual intracanalicular components. Indeed, the initial publication on cystosarcoma phyllodes by Johannes Müller referred to this tumor as giant intracanalicular fibroadenoma. Thus, when one is confronted by a huge encapsulated tumor with gigantiform intracanalicular projections, no uncertainty exists as to the applicability of the term, cystosarcoma phyllodes. These tumors, however, descend from this level of great mass until they are only a few centimeters or less in diameter. The smaller tumors, nevertheless, may present coarser than usual intracanalicular protrusions whose connective tissue portions are more cellular and whose overlying epithelium is more proliferative than that seen ordinarily in intracanalicular fibroadenoma. The question of terminology is provoked and in this laboratory the term "miniature cystosarcoma phyllodes" has been adopted. It is thought that this is more than a pure academic word problem since the tumors have at least a limited capacity for recurrences and these can assume malignant form. An added feature is that they are likely to occur at an older age than is expected for fibroadenomas in general. Compactly stated, the differences between intracanalicular fibroadenoma and cystosarcoma phyllodes concern size and cellularity. In passing it is mentioned that the term cystosarcoma phyllodes without qualification should not denote a malignant tumor. The term is in itself an unfortunate one. Certainly all giant intracanalicular fibroadenomas are not malignant clinically or histologically and when the synonym cystosarcoma phyllodes is used it should imply a benign tumor unless further qualified as malignant or malignant variant.

When a giant intracanalicular fibroadenoma passes into a malignant phase the change involves the connective tissue and not the epithelium in the great majority of cases (Fig. 24). Observation of a considerable number of tumors in an early phase of malignant transformation is the basis for this belief. In the exceptional case both types of cells participate in the malignant process and it would be proper here to speak of true adenosarcoma or carcinosarcoma, that is, adenosarcoma in the derivative sense. Supporting this view of histogenesis is the clinical behavior of the tumors. Those tumors growing as spindle- and polyhedral-cell sarcoma customarily cause death resulting from bulky lung metastases and do not yield axillary node metastases. Cases that develop node metastases are those in which malignant epithelial characters are demonstrated.

A very small number of these tumors develop bizarre structural patterns which include those of squamous carcinoma and osteogenic sarcoma with formation of atypical bone and cartilage.

If a histologic diagnosis of the malignant phase of these tumors is made, there are certain therapeutic implications. If the tumor contains malignant epithelial cells, radical mastectomy is needed. If painstaking study reveals only malignant connective tissue cells, simple mastectomy may be employed. If doubt exists on these points, as sometimes it does, the radical procedure seems a prudent course. In all probability this should always be done when the

tumor has extended beyond its capsule. Confinement within the capsule is naturally a favorable factor but we have witnessed the development of lung metastases when there was no demonstrable invasion of adjacent breast tissue, presumably the result of blood stream invasion within the body of the tumor.

When the common intracanalicular fibroadenoma undergoes malignant change it usually does so in a fashion converse to that usual in cystosarcoma phyllodes. Hence it is the epithelial portion that is concerned rather than connective tissue component. This cannot be regarded as an invariable rule but is a major trend. Malignant fibroadenomas are among the rarest of malignant neoplasms of the breast, somewhat less frequent than the malignant variant of cystosarcoma phyllodes. It may be that malignant fibroadenomas are commoner than can be demonstrated pathologically since a small fibroadenoma could become completely overgrown and obliterated by the malignant tumor cells. On the other hand, a carcinoma developing adjacent to a fibroadenoma can invade the substance of the benign tumor so that a false impression of its origin in that location is imposed. Admittedly, the issue of origin cannot be stated with certainty in some cases.

If the malignant alteration of a fibroadenoma is met with in an early phase, confined to the lining epithelium, or at most not extending beyond the capsule, the disease can be controlled by local excision or simple mastectomy depending upon the extent of the change. With infiltration radical mastectomy becomes necessary.

REFERENCES

1. Foot, N. C.: A Simpler Classification of Mammary Tumors, Arch. Path. 33: 905, 1942.
2. Foote, F. W., Jr., and Stewart, F. W.: Lobular Carcinoma in Situ, Am. J. Path. 17: 491, 1941.

A TECHNIQUE FOR RADICAL MASTECTOMY*

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BECAUSE radical mastectomy is an extensive surgical procedure in which a series of related regional dissections are required, it is only natural that many different techniques have been developed during the fifty years that the operation has been done. A number of these techniques have emphasized different skin incisions, and some surgeons plan their whole procedure in relationship to the limitations of the skin incision. We believe that it is far more important to emphasize certain principles which are basic in the surgical attack of all malignant disease. Our purpose in describing another method for radical mastectomy is to stress the importance of these principles and to illustrate how they may be applied at every stage of this complicated operation.

The history of the development of the operation has been well described by Willy Meyer[1] and by Cooper[2] and the reader will find their papers well worth studying. Both Halsted and Willy Meyer, who independently devised the modern operation half a century ago, changed and improved their respective techniques as time went on. The operation evolved in their hands until both operators emphasized four common principles:

1. Excision of the skin over the whole breast, covering the defect which remained with a Thiersch graft
2. Excision of both pectoral muscles
3. Complete axillary dissection
4. Removal of the excised tissues in one block.

Since their day, improvements in anesthesia and in methods for the avoidance of shock have made extensive surgical dissections safer. It is today possible to carry out with a reasonable degree of safety an even more radical mastectomy than that which Halsted and Willy Meyer performed. In our own surgical attack on carcinoma of the breast we have followed the fundamental principle that the disease, even when confined to operable limits, is such a formidable enemy that it is our duty to make our dissection as radical as possible. By this we mean that today we attempt to remove as much tissue from the chest wall and the axilla as we dare, without unreasonable danger to the patient's life and interference with thoracic and arm function. Just what these limits are we shall attempt to describe. We eschew at the outset all temptation to compromise with carcinoma of the breast by limiting our operation in any way or by doing simple mastectomy. In the face of the proved fact that carcinoma of the breast that has metastasized to the axilla

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has been cured by radical mastectomy, the performance of simple mastectomy in a patient who can tolerate a radical operation is nothing less than surgical cowardice.

A second fundamental principle which we emphasize in operating upon cancer of the breast is gentleness. We take great care not to press upon the tumor. We avoid traction on the breast. All of our manipulations are as gentle as possible. In our microscopic studies we have seen emboli of cancer cells in the lymphatics and in the peripheral sinuses of lymph nodes often enough to be convinced that such emboli may be set free by rough operating and implanted in the wound.

Our own technique for radical mastectomy has been based upon the Halsted operation, but many of the details are derived from the technique of Dr. George H. Semken. His carefully planned and meticulous methods of surgical attack in several forms of cancer have been our inspiration for special emphasis on this form of surgery. We must acknowledge also our indebtedness to Dr. Allen O. Whipple for apprenticeship in silk technique, which adds, we believe, to the delicacy and exactitude of radical mastectomy.

SELECTION OF THE PATIENT

In a recent publication,[3] we have dealt in some detail with the question of operability, presenting a series of criteria for selecting the operable cases. Within the limits of these criteria we believe that women of all age groups with carcinoma of the breast, who are in good enough general condition to run the risk of major surgery, should be treated by radical mastectomy. With such a formidable disease as carcinoma of the breast there is little place for compromise. The operation must be done if the patient can stand it. With proper precautions to avoid shock we have found that we can carry out our complete radical mastectomy with safety upon women in their late seventies and upon women with severe hypertension or diabetes. Patients with severe asthma or chronic bronchitis give us some trouble in the form of respiratory complications, but even with these, operation is certainly indicated.

THE ANESTHESIA

For the type of radical mastectomy which we perform we need a method of anesthesia which will maintain the patient at a relatively superficial plane of anesthesia over a period of between five and six hours of operating. Muscle relaxation is not required. We do not mind, in fact, if the patient stirs slightly now and then, for this assures us that she is lightly anesthesized. Prolonged deep anesthesia is shocking and hazardous.

Avertin given by rectum is the basic anesthetic which in the past has best met our needs. It is important to precede the basic anesthesia by at least one hour with premedication which will allay the patient's apprehension. We give 10 mg. of morphine and 0.4 mg. of scopolamine. The avertin is always supplemented by nitrous oxide or ether, and by additional doses of morphine given at intervals during the course of the operation.

We do not give avertin to patients with marked hypertension, because we fear that the sharp fall in blood pressure which the drug produces may cause cerebral injury. We do not use it when there is hepatic or renal damage because of the danger of improper elimination. Cyclopropane or ether is preferable in both of these types of patients.

Recently we have been using with satisfaction a combination of pentothal and nitrous oxide. This anesthesia has the advantage of avoiding the initial drop in blood pressure which is noted with avertin. After pentothal, moreover, the patients waken more quickly and are able to take fluids sooner. The total amount of pentothal should be kept as low as possible.

THE POSITION OF THE PATIENT ON THE OPERATING TABLE

There are certain details regarding the position of the patient on the operating table which are worth mentioning. Both arms are outstretched. The skin of the one on the tumor side is, of course, prepared down to the elbow, and the whole arm wrapped in sterile towels so that its position can be changed without breaking its sterility. It is then laid outstretched upon a narrow arm board. The other arm is fastened down to an arm board, and is used for blood pressure readings and for intravenous medication.

The operating table is raised high enough so that when the operator stands erect the operative field is at elbow level. Many an operator works with the table too low, requiring him to bend over. His head gets between his field and the overhead light, and in long operations, such as we are here describing, his back is strained.

The operative table is tilted laterally, raising the side being operated upon about 30 degrees. This makes the lateral chest wall more accessible, and facilitates the dissection of the lateral skin flap, which is the first step in our operation.

STEP 1. THE DISSECTION OF THE SKIN FLAPS

We begin by outlining the incision on the skin, using a steel pen and methylene blue for ink. The extent of the skin excised varies with the position and size of the tumor but it is governed by two basic principles. We include the skin over the whole of the protuberant breast (Fig. 1). An additional area of skin is included if the tumor is excentrically situated. When it is in the upper outer sector of the breast, for instance, we include an additional area of skin over the anterior axillary fold. We try to place the line of skin incision at least four fingerbreadths, that is about 7 cm., beyond the edge of the palpable tumor. When the tumor is situated high in the upper outer sector this is sometimes difficult to do for we must retain enough of a skin flap to cover the axillary vessels, so we place our incision a little closer to the edge of the tumor. Other situations of the tumor in the breast do not limit our skin removal. Thus, for tumors of the lower inner sector we include a considerable area of skin over the upper abdomen, extending sometimes to the midline or across it.

We do not plan the extent of skin removal with any reference to closing the wound (with the single exception just mentioned of tumors high in the upper outer sector). We know that we can cover a defect of any size with a skin graft, so we sacrifice as much skin as we think desirable from the viewpoint of curing the carcinoma. The result has been that in every instance we have had a defect of varying size left when the flaps are finally approximated. Since we know at the outset that we are going to have to do a skin graft we are not tempted to skimp in the matter of sacrificing skin.

The actual outline of the skin incision is made by drawing a circle around the breast and the tumor. The circle is then transformed into a vertical incision by pointing it below with a line drawn in the direction of the umbilicus and above with a line drawn approximately in the strap line over the shoulder to a point slightly cephalad to the clavicle.

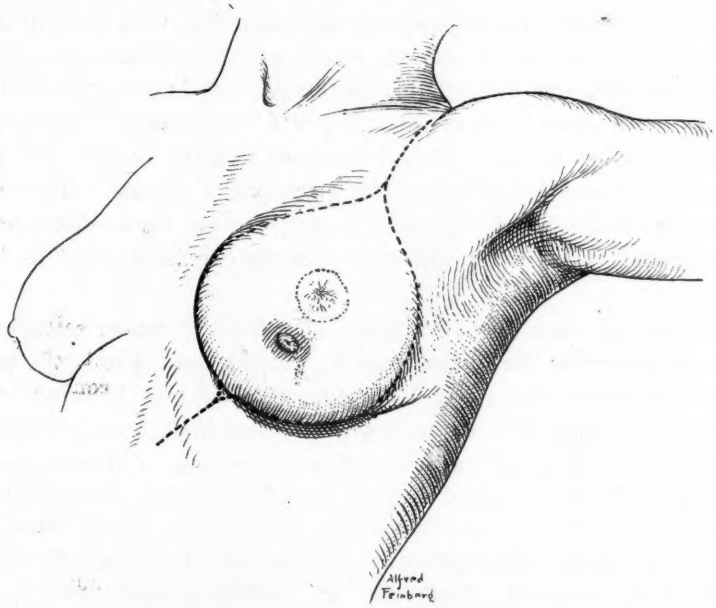

Fig. 1.—The outline of the skin incision.

We formerly carried the upper end of the skin incision out onto the arm over the anterior aspect of the pectoral fold as in the original Halsted and in Willy Meyer's modified (1898) technique. This makes the accurate dissection of axillary flap a little easier, but we have found that this extension onto the arm is by no means necessary. If the incision is carried straight up along the strap-line high up on the shoulder, entirely adequate exposure of the axillary portion of the lateral flap can be obtained with a little careful retraction. The scar is then hidden under the shoulder strap, and the patient can wear a sleeveless dress or a bathing suit.

The worst mistake that the surgeon can make, from the point of view of arm function, in planning the skin incision for radical mastectomy, is to carry the upper end of the incision into the axilla. A vertical band of scar tissue

across the axilla is the inevitable result, and arm motion is restricted. Willy Meyer's original incision extended into the axilla, but he soon realized its disadvantage and changed it.

Transverse incisions are to be avoided because they do not provide adequate exposure of the axilla.

All types of incisions which involve the shifting of flaps to cover the defect that remains when a wide removal of skin is carried out are impractical, because they do not do away with the necessity for skin grafting some area and they further prolong an already lengthy operation.

We dissect back the lateral skin flap first. The incision is made through the skin only, down to the superficial layer of the superficial fascia (Fig. 2). This fascia is delicate but distinct. Over the lower part of the chest wall it is considerably thicker than over the upper part, but with careful hemostasis it can be identified all the way to the upper edge of the operative field at the level of the clavicle. Superficial to this fascia there is only the skin, with its dermal glands and small blood vessels. Beneath it lies breast tissue interspersed in a variable amount of fat. Close beneath the fascia lie the relatively large thin-walled superficial branches of the perforating vessels. They might be called the subfascial blood vessels. Accompanying these blood vessels are lymphatic vessels, which drain the skin over the breast as well as the breast itself.

It is important from the viewpoint of adequate cancer surgery to keep the plane of dissection just superficial to this fascia. First, we wish to be certain that all breast tissue will be removed. We know from our pathologic studies that carcinoma often extends widely throughout breast tissue and that not infrequently it is found as new and separate foci in remote parts of the breast. Breast tissue extends far more widely over the chest wall than the protuberant breast itself. As a thin layer beneath the fascia which we have been describing, breast tissue may be found from the edge of the sternum around the chest wall very nearly to the latissimus dorsi muscle, and from just below the clavicle down to the inframammary fold. It may extend high into the axilla. The surgeon must be certain of removing all breast tissue, and the way to do it is to dissect superficial to the fascia. Second, dissection in this plane will remove the lymphatics accompanying the subfascial blood vessels, one of the routes along which breast carcinoma spreads.

From the viewpoint of surgical convenience also, it is wise to dissect superficial to the fascia. In so doing, the troublesome subfascial vessels will not be cut and the flap can be dissected up leaving hardly any bleeding points on its surface. Good hemostasis makes the dissection more accurate as well as less shocking.

It has been our custom to begin the dissection at the caudad end of the lateral flap and to work toward the cephalad end. The flap is retracted with light sharp, single-pronged hooks which we have devised for this particular purpose. They do not injure the skin as do the various types of compressive

or double-toothed clamps usually employed. In order to provide gentle countertraction in a medial direction on the breast tissue and fat that is being dissected off the skin flap, a series of curved hemostats are placed along the lateral edge of the skin being removed with the breast, clamping the skin edge to a protecting towel which isolates it from the operative field. The handles of the hemostats are tied together in two groups and used as retractors (Fig. 3). In this way rough handling of the tumor area itself is avoided.

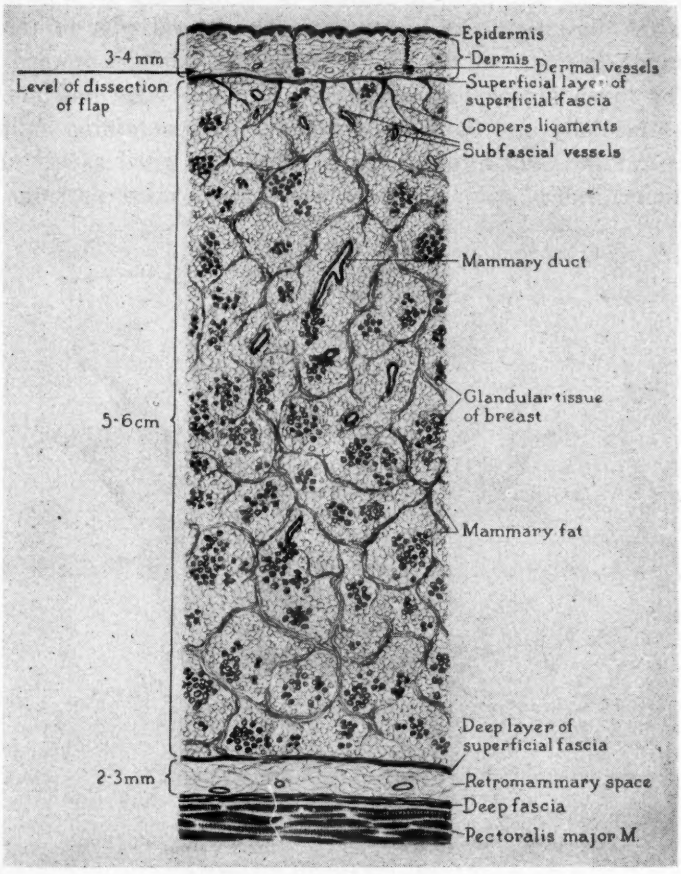

Fig. 2.—Diagrammatic cross section through the breast to show the level of dissection of the skin flaps.

Along the caudad portion of the lateral flap the dissection is carried down over the abdomen until a line about four fingerbreadths, or 7 cm., caudad to the inframammary fold is reached. We assume this to be a safe distance from possible carcinoma and turn our plane of dissection directly in toward the body, incising the superficial fascia and exposing the deep fascia over the rectus and external oblique. This gives us what Semken has aptly called a *red line* at the edge of the dissection. It is a definitive guide to what is to be removed. Carried all around the edge of the operative field as the flaps are dissected back, it avoids confusion during later stages of the operation.

We do not remove the rectus fascia except in cases where the tumor is situated in the lower half of the breast. Handley's pathologic evidence[4] of the permeation of this fascia with carcinoma was obtained from far-advanced cases of the type which we would classify today as inoperable.

The red line is carried laterally and cephalad along the base of the skin flap exposing the external oblique and the serratus anterior muscles, and finally reaching the edge of the latissimus dorsi muscle near a point where it crosses the sixth digitation of the serratus. The lateral edge of the latissimus becomes a guide to the operator as the dissection proceeds toward the axilla. Care must be taken not to lose sight of the muscle edge and not to dissect either too far medially into the dangerous carcinoma-containing axillary tissues or needlessly far laterally into the tissues over the dorsal aspect of the latissimus. These errors are easily made, particularly in obese patients.

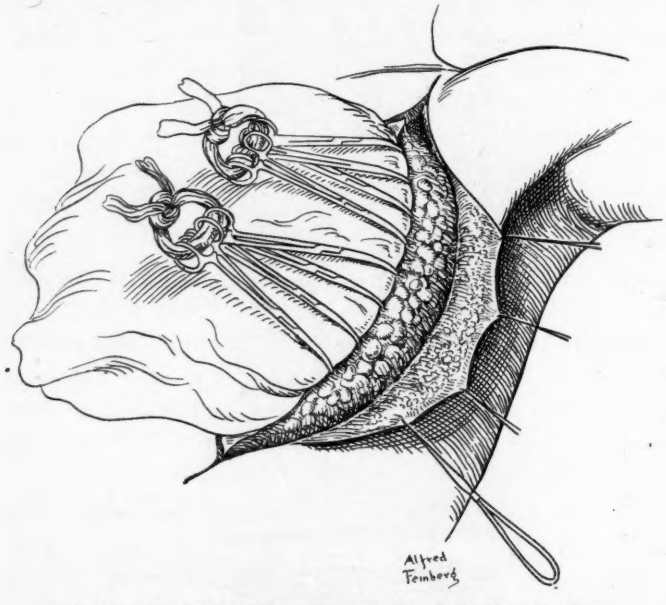

Fig. 3.—Beginning dissection of the lateral skin flap.

At a point about three-quarters of the way upward along the lateral flap this dissection along the latissimus is stopped. The cephalad portion of the skin flap is then dissected up, baring the pectoralis major muscle. This leaves a bridge of axillary fat attached to the skin flap (Fig. 4). This tissue is dissected off of the axillary skin, leaving its apocrine glands exposed. These are seen as small reddish-brown foci of tissue, interspersed with the roots of hairs, lying immediately beneath the skin over the center of the axilla. They are a good guide for the operator in this region, for unless they are exposed the skin flap is being cut too thick. As a final step in the elevation of the lateral flap the dissection is carried cephalad along the white tendon of the latissimus, and then up across the axillary vein (Fig. 5). In this dissection along the

white tendon, carrying our so-called red line up across the axillary vein, several small intercostobrachial nerves and accompanying arteries and veins which cross over the white tendon at right angles to it are encountered. They must be isolated, clamped, cut, and tied with care, otherwise the operative field becomes soiled with blood and good exposure of the axillary vein becomes more difficult.

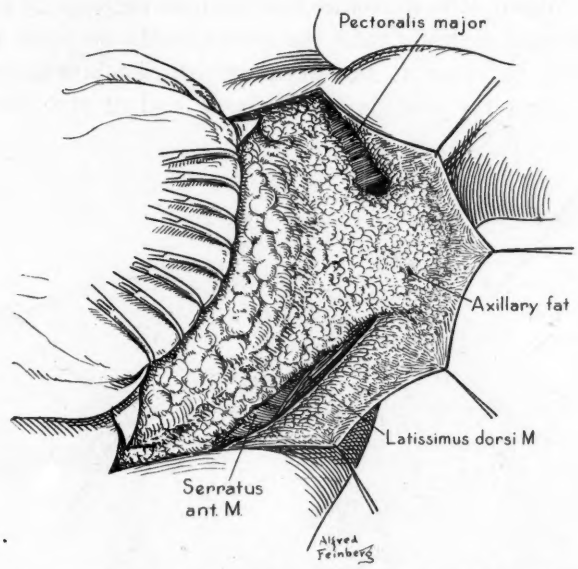

Fig. 4.—Dissection of the lateral skin flap at a later stage.

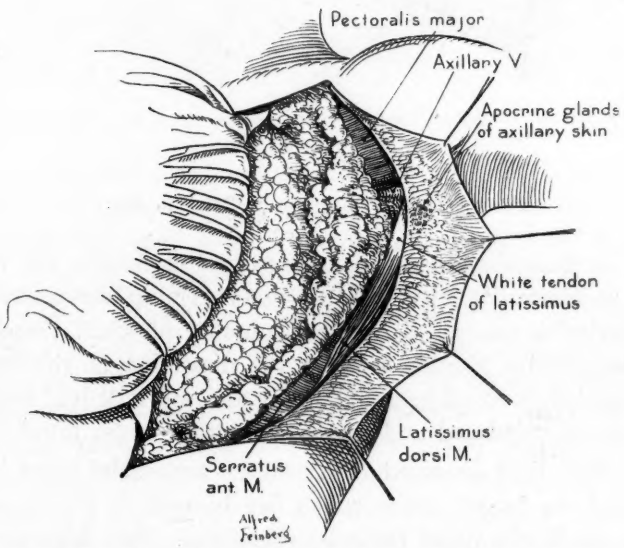

Fig. 5.—Dissection of the lateral skin flap completed.

The hemostasis along the whole length of the axillary flap is now carefully checked, and the flap is replaced against the chest wall so that it will not be angulated and its nutrition interfered with. It is covered with a moist towel. The breast is allowed to fall laterally and the operating table is turned back to a level plane, preparatory to the dissection of the medial skin flap.

The medial skin flap is dissected back with the same technique used for the lateral flap. Again, it is convenient to begin at the caudad end of the flap. The dissection crosses medially over the rectus fascia to reach the midline of the sternum. The red line at the periphery of the operative field is then carried upward along the midline to the inner end of the clavicle (Fig. 6).

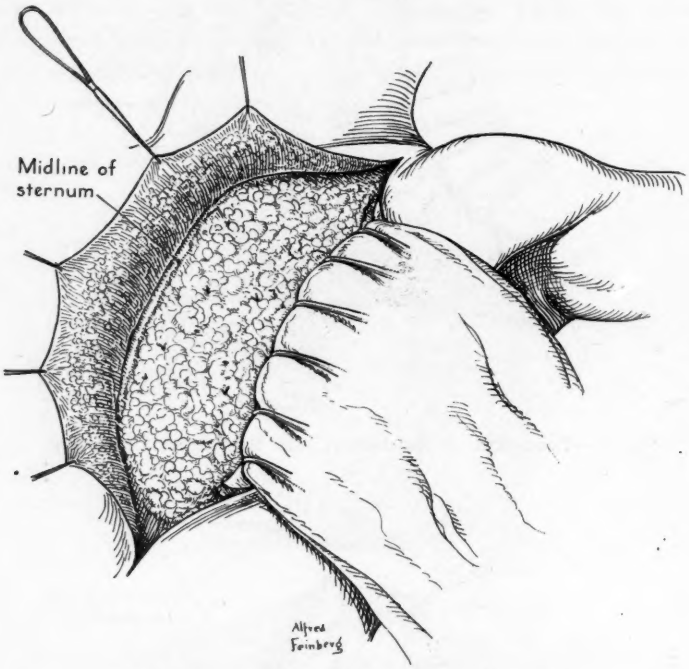

Fig. 6.—Dissection of the medial skin flap.

The direction of dissection then turns laterally and follows the lower edge of the clavicle, encountering fibers of platysma coming down from the neck. Along this clavicular line of dissection a number of small vessels crossing it at right angles require ligation. When the dissection of this medial flap is completed a careful check of hemostasis is made, and it is laid back in place so that it will not be angulated and is covered with a moist towel.

The skin flaps thus dissected up from the superficial layer of the superficial fascia and the breast tissue which lies beneath it are thinner than the flaps that are cut in the usual radical mastectomy. Our flaps are only 3 or 4 mm. thick and consist of the skin covered with only a delicate layer of fine fat lobules. Halsted, in his original operation, dissected this kind of a flap

over the axilla, for he was a good gross pathologist and realized that a thick flap in this region implied dissection perilously close to axillary nodes. Elsewhere, however, his flaps were thick, the incision being carried, in his own words,[5] "through the fat." His original illustration (Fig. 7), which we have reproduced, shows the thin axillary flap turned back, and the deep incision through the fat down to the muscle plane around the periphery of the operative field. In defense of Halsted's technique it must be added that his excision was a very wide one, leaving such a large defect on the chest wall that skin grafting was regularly required.

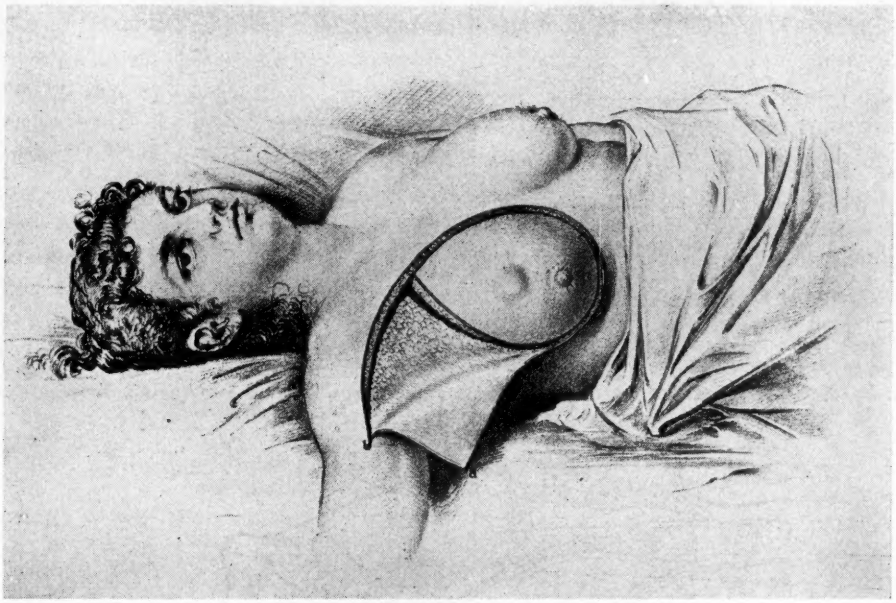

Fig. 7.—The skin flaps as shown in Halsted's original illustration.

Most modern operators are much less radical. Their excision is so limited that the edges of the flaps can be brought together and the wound closed. Moreover, the usual practice is to cut thick flaps around the whole operative field, omitting even the dissection of the thin axillary flap that Halsted emphasized. In Fig. 8, reproduced from an illustration of a contemporary operator's technique, these thick flaps are shown. The skin incision is carried almost directly down through the fat and mammary tissue to the muscle plane, exposing the pectoralis major medially and the serratus muscle laterally. The flaps thus cut bear coarse lobules of fat and are several centimeters thick in most patients. Such flaps are easily and quickly made, while the dissection of our thin flaps is a tedious procedure, requiring between one and one-half hours and two hours. In our technique (Fig. 9) the pectoral and serratus muscles are not laid bare, except where our red line crosses them at the periphery of the operative field. The line of dissection must be exact and the

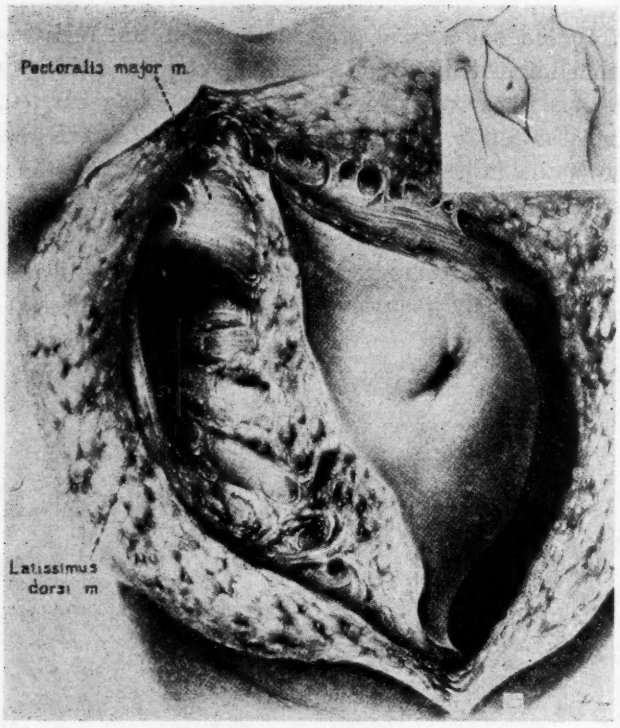

Fig. 8.—A widely used technique for cutting the skin flaps. (From Harrington, S. W.: Carcinoma of the Breast, J. A. M. A. 92: 208, 1929.)

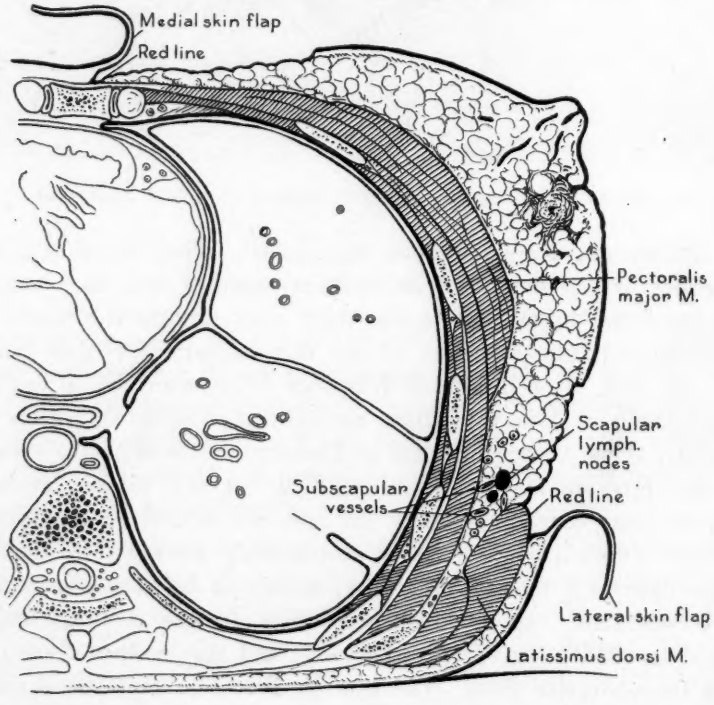

Fig. 9.—Cross section showing the method of dissecting the skin flaps.

tissues must be handled gently, otherwise the viability of the flaps will be compromised. We think of this method of dissecting the skin flaps as the logical development of Halsted's original plan. The ultimate value of the method will, of course, depend upon the demonstration of a decreased incidence of local recurrence.

STEP 2. THE DISSECTION OF THE PECTORALIS MAJOR FROM THE ARM

The dissection then goes forward at a deeper plane, and we begin by severing the attachment of the pectoralis major to the arm. The surface of the pectoralis at the base of the lateral skin flap over the arm is exposed. With the aid of lateral retraction on the flap the dissection is carried laterally, clearing the muscle surface until the cephalic vein, separating the deltoid from the pectoralis, is identified and exposed. The vein is followed out along the deltoid-pectoral groove until the apex of the pectoralis at its attachment to the humerus is reached. The muscle is then cut across at a right angle to the direction of its fibers, close to its attachment. Only about a centimeter of muscle remains to form a stump which is not bulky and which contains but two or three small vessels requiring clamping and tying. Most operators force a finger beneath the muscle and elevate it before severing it. We do not find this necessary.

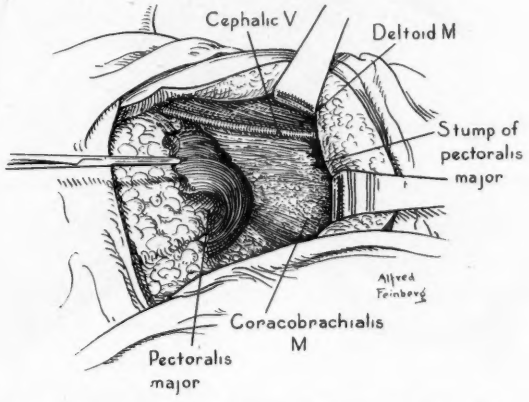

Fig. 10.—Dissection of the pectoralis major from the arm.

When its attachment to the humerus has been cut the pectoralis is dissected free from the deltoid along the cephalic vein and retracted medially, care being taken to clamp and tie the small branches emerging from the pectoralis to enter this vein. The dissection brings the coracobrachialis and the deep pectoral fascia covering the deep structures of the axilla into view (Fig. 10). The operator may be tempted to save the clavicular portion of the pectoralis, splitting the muscle between its pectoral and clavicular divisions. This maneuver has two disadvantages. The line of cleavage is a poor one and bleeding is difficult to control. More important is the fact that leaving the clavicular portion of the muscle in situ hinders proper access to the apex of the axilla.

There are several atypical muscles of the pectoral region, and it is perhaps worth while mentioning the one most frequently encountered and most likely to confuse the operator, the so-called *axillary* pectoral muscle. Eisler's[6] drawing of it is reproduced here (Fig. 11). As a short muscular band of varying thickness, it arches from the white tendon of the latissimus dorsi up over the axillary vessels and nerves to join the tendon of the pectoralis major at its attachment to the humerus. This muscle is well developed in the anthropoid apes and is present in about 7.7 per cent of human subjects of European stock. In the dissection that we are describing it must, of necessity, be severed.

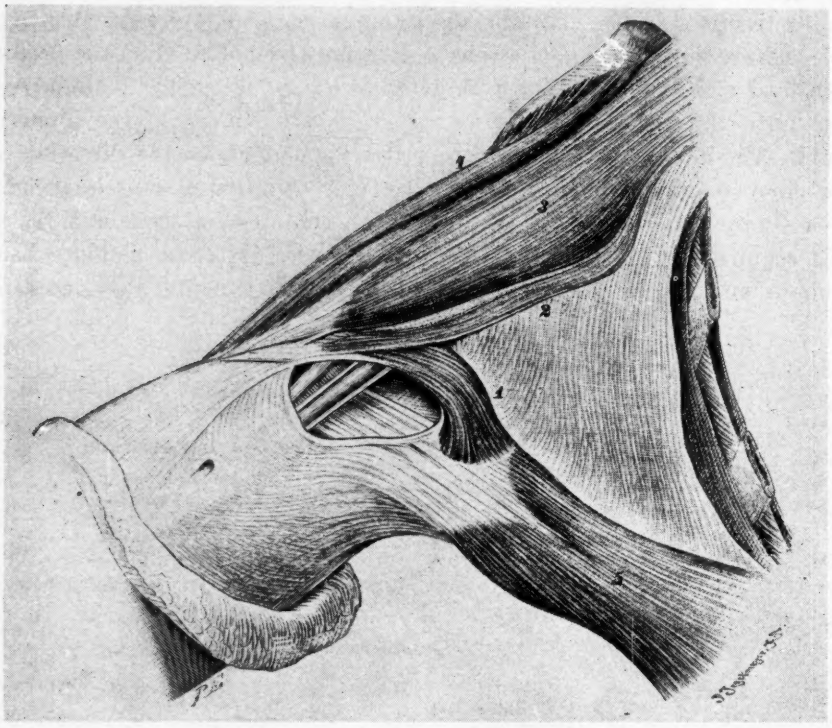

Fig. 11.—Atypical axillary muscles. *1*, Axillary pectoral muscle; *2*, pectoralis quartus muscle; *3*, pectoralis major muscle, sternal portion; *4*, pectoralis major, clavicular portion; *5*, latissimus dorsi muscle. (From Eisler.)

STEP 3. THE DISSECTION OF THE PECTORALIS MAJOR FROM THE CLAVICLE

As the dissection of the pectoralis major away from the deltoid is carried medially along the cephalic vein to the apex of the triangle which the deltoid forms with the clavicle, the thoracoacromial vessels come into view. The pectoral branches of the thoracoacromial artery, the accompanying veins, and the lateral anterior thoracic nerve pierce the deep pectoral fascia just above the medial edge of the pectoralis minor, and stretch across the operative field to enter the deep surface of the pectoralis major. They should be carefully isolated, clamped, cut, and tied.

The pectoralis major is retracted caudad exposing the deep pectoral fascia. Beneath this strong fascia lie the pectoralis minor, the axillary vessels and nerves, and the lymphatics and lymph nodes in which we are particularly interested. All of our dissection at this stage of the operation is carried out superficial to this fascia.

The dissection is then carried medially, severing the attachment of the pectoralis major to the clavicle by cutting across its fibers parallel to and about 1 cm. below the lower edge of the clavicle. Leaving a little of the muscle on the clavicle in this way makes it easier to clamp and tie the series of small vessels which are severed. The first interspace is exposed, as the muscle is cut away from its origin on the clavicle (Fig. 12).

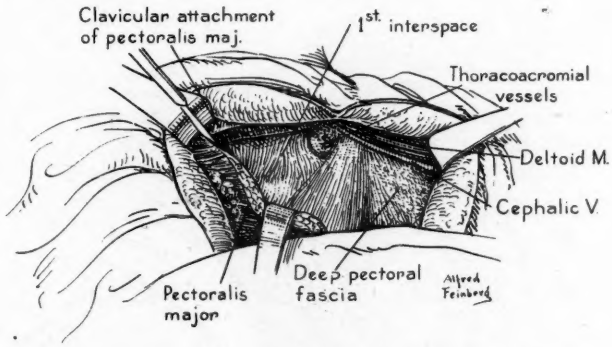

Fig. 12.—Dissection of the pectoralis major from the clavicle.

STEP 4. THE DISSECTION OF THE PECTORALIS MAJOR FROM THE CHEST WALL

In this step the pectoralis major is severed from its broad origin from the sternum, ribs, and the fascia of the oblique muscle, allowing the whole operative specimen to fall laterally to the patient's side. This can be the bloodiest and most shocking part of the operation unless it is done with care and exactitude.

The dissection is begun by clearing the first interspace down to the fascia over the intercostal muscles, at a point a little lateral to the medial end of the origin of pectoralis major along the clavicle which was severed in Step 3. The thick body of the pectoralis major muscle is then elevated from the second rib with a small retractor or with the finger, developing a plane of cleavage between this muscle and the thoracic cage. With the muscle thus slightly elevated and tensed its detachment from its broad origin from the inner end of the first interspace, the cartilage of the first rib, and the manubrium is begun. Several branches of the first perforating artery and vein will be encountered as this broad muscle attachment is cut through. The first perforators themselves usually come into view near the caudad edge of the interspace, as they arch up over the second costal cartilage. They should be carefully isolated, clamped, cut, and tied. A much smaller perforating vessel, the first

of a series of minor perforators which emerge parallel to and at a point 3 or 4 cm. lateral to the main perforating vessels, should also be clamped, cut, and tied.

The dissection is then carried caudad, severing the pectoralis from its attachment to the sternum and ribs, and identifying and clamping the perforating vessels as they come into view. Their position in the lower interspaces is variable; sometimes they emerge just below and sometimes just above a costal cartilage. The intercostal spaces should be meticulously cleared of all fat and areolar tissue as the dissection proceeds (Fig. 13). As the thoracic cage is thus denuded it should be covered with warm moist compresses or a towel in order to prevent drying of the tissues and consequent shock. The operative specimen is allowed to fall laterally and is similarly covered with a protecting towel.

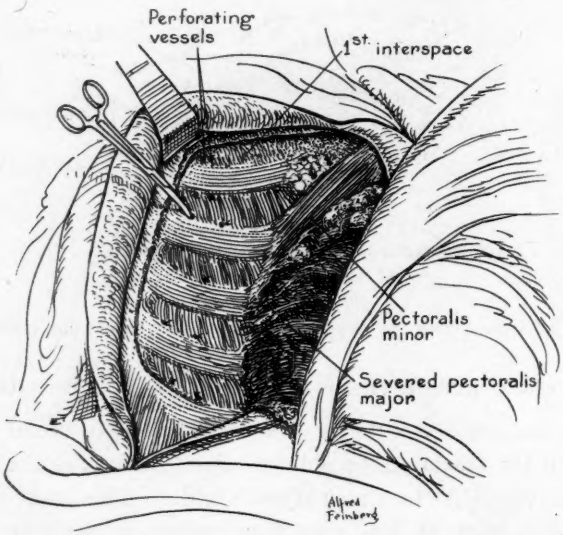

Fig. 13.—Dissection of the pectoralis major from the chest wall.

When the dissection of the pectoralis major from the chest wall has been carried laterally to a point where the fan-shaped edge of the origin of pectoralis minor comes into view, it should be discontinued. This is a convenient point at which to pause and tie the many clamped vessels, getting rid of the mass of clamps that have accumulated as the chest wall has been cleared. The pectoralis minor must now be dealt with in a separate step.

STEP 5. SEVERING THE ATTACHMENT OF THE PECTORALIS MINOR

An incision is made through the deep pectoral fascia along the lateral edge of the pectoralis minor muscle near its cephalad end where it becomes tendinous. A finger or a small retractor is gently inserted beneath the muscle, elevating it from the axillary vein and the cords of the brachial plexus which lie directly beneath it.

At this point in the dissection it is desirable to identify, clamp, and cut a tiny muscular branch of the thoracoacromial artery, and its accompanying vein, which usually enters the pectoralis minor along its medial edge near its tendinous end. Although these vessels are very small they bleed freely and obscure the operative field if they are torn in the process of severing the minor.

With the muscle slightly elevated it is cut across as high as is convenient, usually at a point about 2 cm. from its attachment to the coracoid process (Fig. 14). One or two small vessels are severed in its deeper muscular portion. These should be carefully clamped and tied.

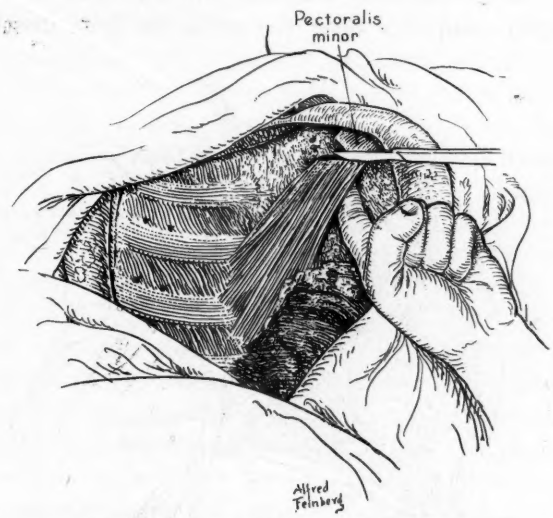

Fig. 14.—Severing the attachment of the pectoralis minor.

The minor is then turned back, exposing its deep surface and baring the areolar tissue covering the axillary structures. Since our axillary dissection is a separate and later step in our operation, we take care not to disturb these axillary structures at this stage. The vessels and nerves which emerge from the areolar tissue of the axilla and stretch across it to enter the deep aspect of the minor are clamped and cut close to the muscle. This frees the muscle so that it can be retracted laterally, giving access to its origin from the third, fourth, and fifth ribs.

STEP 6. THE DISSECTION OF THE PECTORALIS MINOR OFF THE CHEST WALL

The pectoralis minor is cut from its origin from the ribs and from the aponeurosis covering the intercostal muscles, proceeding from the third to the fifth ribs. It has been found convenient to pick up the edge of the muscle with thumb forceps and to retract it away from the edge of each rib as its origins are severed. The pectoralis minor interdigitates with the serratus anterior, and special attention is required to distinguish the deeper layers of the minor from the serratus digitations which lie beneath.

The pectoralis minor is allowed to fall laterally with the other tissues severed from the chest wall and the dissection is continued in that portion of the operative field just caudad to the origin of the minor. In this region the dissection of the specimen off the chest wall should include the careful removal of the fascia over the digitations of the serratus (Fig. 15). Important lymphatic trunks, which we will describe later, lie upon or within this fascia.

This dissection is carried laterally around the chest wall, and the specimen allowed to fall away to the patient's side, until the edge of the latissimus comes into view in the caudad part of the field. It is then desirable to suspend the dissection of the specimen off the chest wall, because its detachment can be more conveniently completed after the axilla has been dissected.

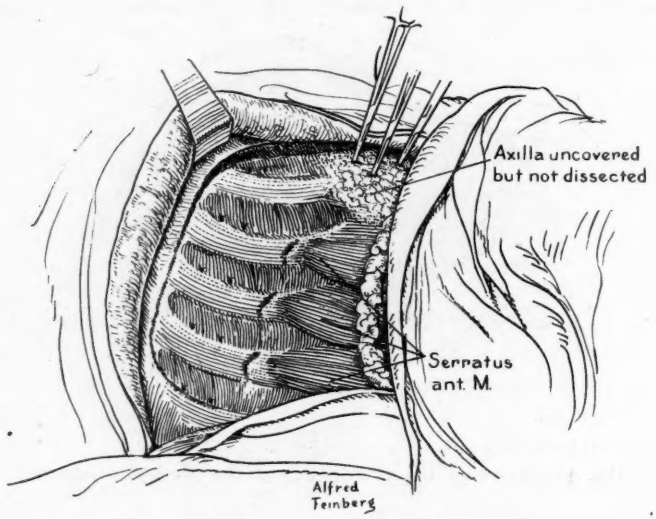

Fig. 15.—Dissection of the breast and pectoral muscles from the chest wall completed.

Before going on to the next stage all clamped vessels on the thoracic wall should be tied, hemostasis checked, and the whole area of denuded thorax carefully covered with moist compresses.

STEP 7. THE DISSECTION OF THE AXILLA

The axilla now lies before the operator like an open book. When the arm lies beside the trunk the axilla may be thought of as a cleft between the shoulder structures and the thoracic wall. When the arm is abducted at right angles to the trunk, however, as in radical mastectomy, the cleft becomes a tetrahedral space, with its apex at the clavicle and its base at the pit of the axilla. The three elongated triangular sides of this space are then formed by the shoulder structures cephalad, the chest wall caudad, and the pectoral muscles ventrally. In the usual technique for radical mastectomy in which the axilla is dissected before the pectoral muscles and breast are removed from the chest wall, the surgeon's access to the axilla is not good because the structures forming its ventral wall (the axillary prolongation of the breast and the fat usually found

in this region, and the pectoral muscles) constitute a bulky mass which tends to slide down into the field of dissection in the axilla. In the technique for radical mastectomy which we are here describing, this bulky mass of tissues is out of the operator's way when he attacks the axilla, for with the dissection of the breast and pectoral muscles off the chest wall they have fallen away to the patient's side. Any surgeon who has compared the ease of access to the axilla with these two different techniques will at once realize the advantage, from this point of view, of our procedure. Instead of having to dissect in the depths of a deep narrow cleft, bothered by the need for constant retraction of the overlying tissues, the surgeon can work at ease without any retraction on a comparatively flattened field.

The objection usually voiced against our technique of excising the breast and pectoral muscles from the chest wall before attacking the axilla is that it increases the chance of distant metastasis. We do not believe that this is the case. The axillary route for metastasis, of course, remains open during the period required to dissect the breast and pectoral muscles from the chest wall, but we do this without any handling of the tumor itself and with only the gentlest kind of retraction on the muscles close to the point at which they are cut from the chest wall. It should be emphasized, on the other hand, that in the usual technique for radical mastectomy in which the breast and the pectoral muscles are retracted medially as they are severed from the chest wall, strong traction on the specimen is required and a considerable degree of pressure is often exerted upon the tumor itself. Even though this takes place after the lymphatic pathway through the axilla has been severed we fear that it may squeeze tumor emboli into lymphatic trunks which still remain, such as those to the internal mammary chain of nodes.

As another objection to our technique of excising the breast and pectoral muscles from the chest wall before attacking the axilla, it has been asserted that we cut across the pathway of lymphatic drainage to the axilla in carrying out the first steps of our operation. A review of the anatomy of the lymphatics of the breast will show, however, that we do not disturb the main lymphatic pathway to the axilla, which is by way of lymphatic trunks which run laterally and upward from the breast to enter the central group of axillary lymph nodes. This pathway is beneath the deep pectoral fascia, which remains undisturbed by the first steps of our operation. We unroof the axilla but we do not enter it.

Because no adequate description of the anatomy of the lymphatics of the breast has been presented in English since Leaf[7] included this information in his excellent little book *Cancer of the Breast: Clinically Considered,* printed in 1912, it seems desirable to include such a description here. The best monographs on the lymphatics are those of Bartels[8] and Rouvière[9] but they are not everywhere available. Tobias'[10] translation of Rouvière's work is unsatisfactory because of the poor quality of the illustrations. Oelsner[11] and Mornard[12] made special studies of the breast lymphatics which are well worth reading. A thorough understanding of this anatomy is of fundamental importance to the surgeon attacking breast carcinoma.

The main collecting lymphatic vessels from the breast are two trunks which leave the subareolar lymphatic plexus, one from its medial and one from its lateral side, and run laterally directly to the central group of axillary lymph nodes or indirectly to the central nodes by way of the external mammary or the paramammary nodes.

There are, in addition, several accessory lymphatic pathways from the breast as follows:

1. The Transpectoral Pathway. The transpectoral lymphatics penetrate the pectoralis major along the course of the pectoral branches of the thoracoacromial artery, and enter the subclavicular group of nodes. Occasionally intermediary lymph nodes are found along these lymphatic vessels, the so-called nodes of Rotter.

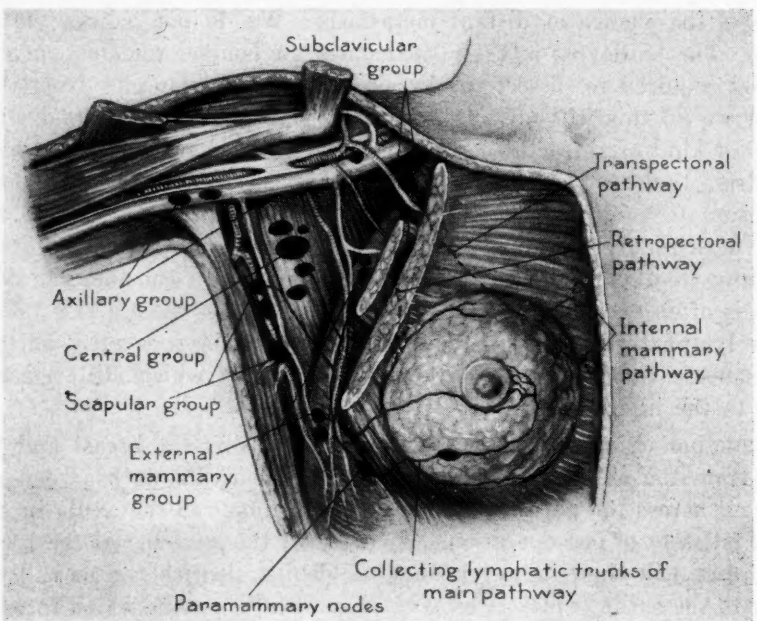

Fig. 16.—The lymphatics of the breast.

2. The Retropectoral Pathway. One or two lymphatic vessels may turn the outer edge of the pectoralis major and ascend either between the two pectoral muscles or beneath the pectoralis minor, directly to the subclavicular group of nodes.

3. The Internal Mammary Pathway. A series of lymphatic vessels directed toward the midline drains the medial portion of the breast. These vessels accompany the anterior perforating branches of the internal mammary blood vessels, and pierce the intercostal spaces near the sternal border to reach the internal mammary chain of nodes. We are inclined to believe that this is an important route of lymphatic drainage, because we see local recurrence of carcinoma of the breast more frequently just at the sternal edge where these

lymphatics pierce the chest wall than almost anywhere else. We have often noted that the superficial branches of the perforating blood vessels, the ones we have designated as the subfascial vessels, are enlarged at the intercostal level of the breast tumor. Presumably this hypertrophy is due to the increased demand that the tumor makes upon the circulatory system. It is not surprising that correspondingly hypertrophied lymphatic vessels may contain tumor emboli which lodge, for some reason, at the point where these vessels pierce the chest wall, and subsequently become evident as local recurrence of the carcinoma at this point.

In addition to the deeper lymphatic trunks which we have been describing, the breast is, of course, drained by regional cutaneous lymphatics. These form a dense network in several planes over the center of the breast. The most superficial of these planes has been called the areolar plexus and corresponds in position to the dermal lymphatic plexus of the skin. The deeper plane is called the subareolar lymphatic plexus and corresponds to the subdermal lymphatic plexus of the skin. The collecting trunks from these lymphatics of the skin over the breast converge toward the axilla and empty into the central group of axillary lymph nodes. They also anastomose freely with the cutaneous lymphatics of the adjacent skin over the upper abdomen, the neck, and, most important of all, over the opposite mammary region. This anastomosis of cutaneous lymphatics across the midline is the path by which carcinoma extends from one breast to the other.

In passing, we should point out that true metastatic involvement of the opposite breast is ordinarily seen only in the late stage of carcinoma of the breast. In most instances in which the opposite breast becomes involved, and the original disease is not far advanced, we believe that the carcinoma in the opposite breast is a new primary tumor.

We have described elsewhere[3] the process by which carcinoma emboli lodge in the dermal or so-called areolar lymphatics, blockade the flow of lymph from the skin over the breast, and make it edematous. When carcinoma emboli have reached this relatively superficial position the disease is far advanced and the chance of cure remote.

Permeation of the cutaneous lymphatics giving the picture of carcinoma en cuirasse is the final stage in many instances.

In these advanced cases, involvement of the lymphatics of the external intercostal muscles which terminate in the posterior intercostal nodes, and in those of the internal intercostal muscles which terminate in the internal mammary nodes, may occur. Under similar circumstances the lymphatics of the rectus sheath and rectus muscle provide a route for metastases to the triangular ligament and nodes at the hilum of the liver. These lymphatic routes and the variegated types of retrograde lymphatic permeation which occur in advanced carcinoma of the breast are not pertinent to our discussion of the technique of radical mastectomy, because the operation should not be done in advanced cases.

The lymph nodes which the surgeon must attempt to excise en bloc in a radical mastectomy number between thirty and forty in younger patients. In old age their number may be considerably smaller and the bulk of lymphoid tissue greatly reduced by fatty replacement. Our drawing (Fig. 16) showing the position of these nodes has been adapted from Rouvière's, and is semi-diagrammatic.

There are five principal groups of nodes, as follows:

1. The Axillary Vein Group. The axillary nodes lie along the lateral portion of the axillary vein, usually on its caudad aspect.

2. The Scapular Group. The chain of scapular nodes lies along the subscapular blood vessels and extends from the lateral thoracic wall to the axillary vein.

3. The External Mammary Group. The external mammary nodes lie along the medial wall of the axilla, outside of or in the fascia covering the digitations of the serratus anterior muscle. The chain extends from the sixth rib to the axillary vein, following the course of the lateral thoracic artery.

4. The Central Group. The central group are the largest of the axillary nodes and they lie embedded in fat in the center of the axilla. They are the nodes most often palpable. They can best be felt by gentle palpation against the lateral thoracic wall with the arm relaxed and adducted, for in this position the deep pectoral fascia is relaxed and the nodes lie against the chest wall.

5. The Subclavicular Group. The subclavicular nodes lie at the apex of the axilla. They are often found as high as the surgeon can carry the dissection, at the point where the subclavian vein disappears beneath the subclavius muscle. The collecting trunks from all of the other groups of axillary nodes empty into these subclavicular nodes, and from the plexus of lymphatic vessels which connects them one with another, one or more large lymphatic trunks arise which pass upward beneath the clavicle to empty into the junction of the jugular and subclavian veins. These large trunks can be plainly seen at the very apex of the axilla, especially where the nodes contain metastases and the lymphatic trunks are enlarged.

All of the nodes that we have been describing lie beneath the deep pectoral fascia which encloses them together with the axillary blood vessels, nerves, connective tissue, and fat, within a delicate yet strong sheath. This fascia has been variously called the suspensory ligament of the axilla, the costocoracoid membrane, the clavicoracoaxillary aponeurosis, etc. We have reproduced Eisler's[13] excellent drawing of it (Fig. 17). Whatever name is given to it, surgeons should recognize its importance as a guide in the dissection of the axilla. As Leaf has pointed out, this fascia gives coherence to the fat and lymph nodes of the axilla and makes their removal in one piece, together with all of the fascia, easier than would otherwise be the case.

The pectoralis minor, in its vertical course across the middle of the axilla, lies between two planes of the deep pectoral fascia. It is, therefore, quite impossible to dissect the axilla adequately without sacrificing this muscle.

Between the cranial edge of the minor and the clavicle is an irregular four-sided space surrounded by bandlike thickenings of the deep pectoral fascia. There is usually a central fossa ovalis in this space providing an opening in the fascia through which the anterior thoracic vessels and the cephalic vein pass.

Between the lateral edge of the pectoralis minor and the coracobrachialis muscle there is a three-sided space covered by a particularly strong portion of the deep pectoral fascia.

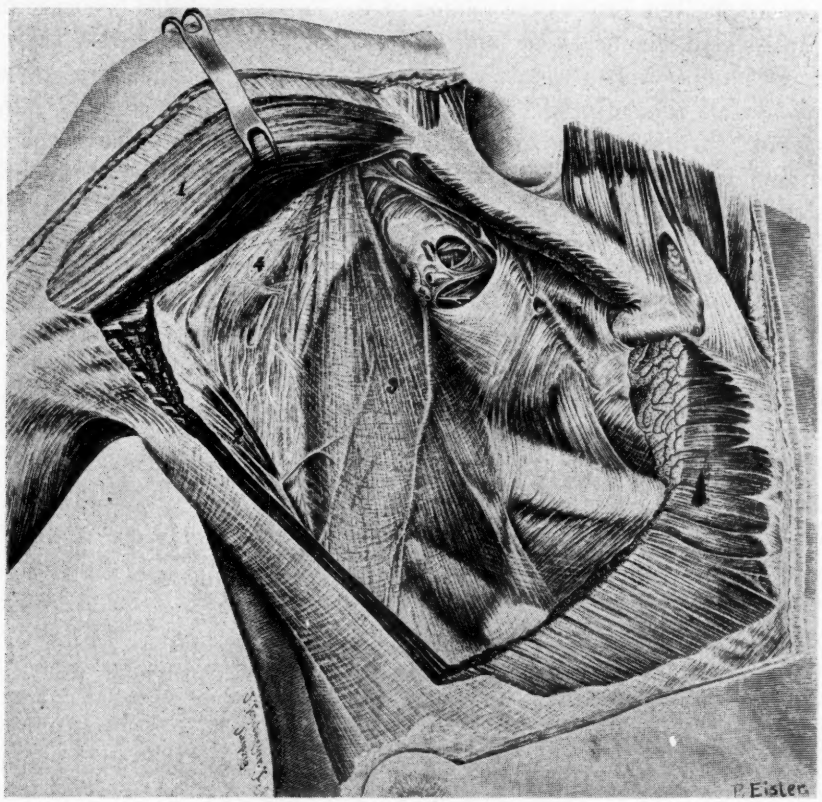

Fig. 17.—The deep pectoral fascia as shown after the pectoralis major has been to a large extent removed. *1*, Deltoid, *2*, pectoralis major, *3*, pectoralis minor, *4*, coracobrachialis. (From Eisler.)

We begin our dissection of the axilla by incising the deep pectoral fascia over the brachial plexus, parallel to and slightly cephalad to the axillary vein (Fig. 18). The fascia is picked up between smooth forceps held by the operator and by his assistant, and incised with a sharp knife. All of our axillary dissection is done with smooth forceps and the knife. We never scrape the axillary contents out with a gauze sponge over the finger as is the custom of some operators; if the nodes contain metastases this is a splendid way to implant carcinoma cells throughout the operative field and to insure local recurrence. We use smooth rather than toothed forceps in our dissection because we fear that toothed instruments may pierce carcinomatous nodes and pick up

and reimplant carcinoma cells. We take care, indeed, to avoid grasping nodes even with smooth forceps. Very little traction is needed and usually it can be exerted through clamps on the specimen side of the vessels that are divided.

The deep pectoral fascia having been incised above the vein, the fascia thus released and the fat and areolar tissue attached to it are dissected caudad, bringing the wall of the vein into view. Its ventral and caudad surfaces are meticulously cleared from the level of the thoracoacromial vessels laterally to the point where the vein crosses the tendon of the latissimus. The branches of the vein are isolated, clamped, cut, and tied as they are encountered. They vary greatly in number and arrangement. Only one thing need be kept in mind: they should all be sacrificed. The axillary vein occasionally divides into two main trunks. These, of course, should both be preserved. We have not found it necessary to sacrifice the axillary vein on account of the extent of the axillary metastases. Proper care in the selection of cases for operation will avoid the necessity for such a radical and futile step, for we are convinced that such cases are incurable.

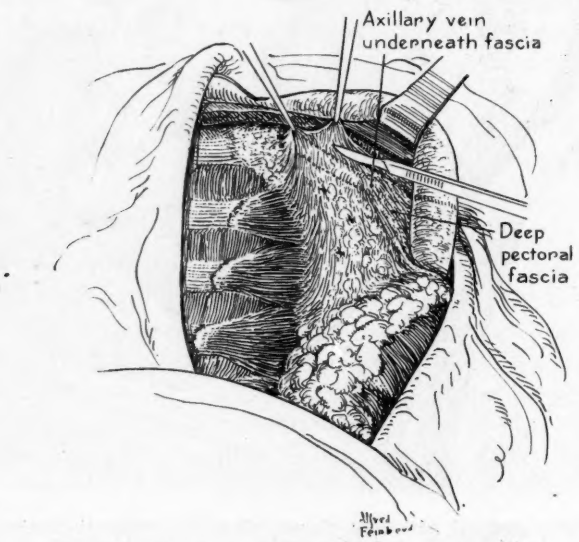

Fig. 18.—Beginning the axillary dissection.

It is not necessary to dissect the fat and areolar tissue overlying the brachial plexus. The axillary lymph nodes are not found lying cephalad to the axillary vein, except in the vicinity of the thoracoacromial vessels. We have occasionally found one or two nodes in this region and it is therefore our custom to clear the stumps of these vessels with care.

A technical detail concerning the dissection of the axillary vein is worth mentioning. At a point from 1 to 3 cm. lateral to the thoracoacromial vessels beneath the portion of the vein uncovered by the removal of the pectoralis minor, the vein is usually crossed obliquely by a small artery and nerve (Fig. 19). The artery enters the deep surface of the pectoralis minor and sometimes

sends a branch onto the adjacent chest wall. Its origin is hidden above and behind the vein where the surgeon does not see it, but it is from a common trunk with the thoracoacromial axis in about one-half of the anatomic subjects we have studied, and as a separate branch from the main artery, 1 or 2 cm. lateral to the thoracoacromial trunk, in the other half of the subjects. It is not described in the anatomic texts which we have consulted, so that we have had to designate it simply as *the artery to the pectoralis minor.*

The nerve which accompanies it is the medial anterior thoracic nerve, which also supplies the pectoralis minor. Both the artery and the nerve are closely applied to the ventral surface of the vein in their oblique course across it, and it is from this fact that their importance to the surgeon arises. Since we strip the axillary vein clean we necessarily remove these two structures which cross over it. A small vein is usually found emptying into the axillary vein just beneath the crossing artery. In isolating, clamping, and cutting the artery and nerve, care should be taken to identify and clamp this small venous branch before it is torn and the operative field soiled with blood. It is possible indeed to dissect the entire axilla without any loss of blood, the great advantage being that the surgeon can see all the time exactly what he is doing.

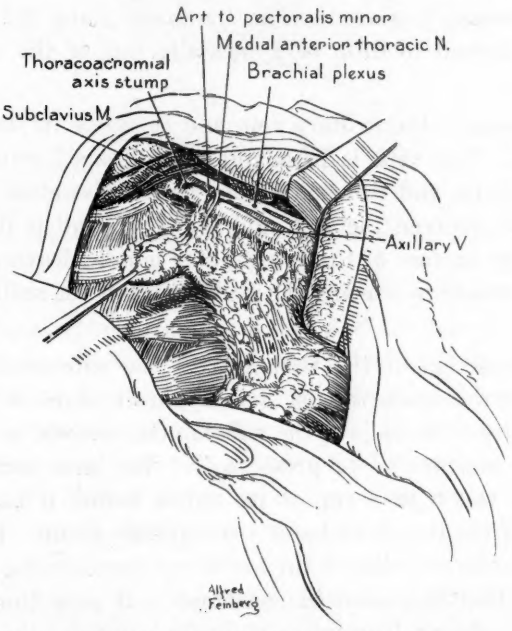

Fig. 19.—Clearing the axillary vein.

Having cleared the ventral and caudad aspects of the axillary vein, we turn our attention to the apex of the axilla. We dissect the fat and areolar tissue off the subclavian vein to the point where it crosses beneath the subclavius muscle. The reflection of the deep pectoral fascia onto the chest wall opposite this portion of the vein is then dissected away from the chest wall to the apex

of the axilla. The mass of fat and areolar tissue thus mobilized in the cleft between the chest wall and the vein contains the highest axillary lymph nodes and the lymphatic trunks that pass upward beneath the clavicle to empty into the venous circulation. A clamp is placed across the apex of the mass as high as possible and it is cut across and ligated in order to avoid backflow of lymph into the wound and to secure the small blood vessels which are usually included within the clamped tissue. A long marking tie is placed around the free end of the mass of apical tissue to orient the pathologist in his study of the specimen.

In order to avoid injury to the long thoracic nerve during the next stage of the axillary dissection, it is now desirable to continue the dissection of the tissues from the chest wall, already begun at the apex of the axilla. The sheet of fascia over the digitations of the serratus anterior is gently retracted laterally and dissected off this muscle. The intercostohumeral nerves spanning the axilla transversely, and the lateral cutaneous branches of the intercostal nerves and their accompanying vessels, are encountered and ligatured, as this dissection is carried dorsally. In the depths of the cleft between the naked serratus digitations and the sheet of fascia retracted laterally, the long thoracic nerve of Bell finally comes into view. It lies in the fat just beneath the surface of the fascia (Fig. 20). An incision is made through the fascia along the lateral edge of the nerve and it is allowed to drop back medially out of the way of subsequent dissection.

We return again to the axillary vein and complete its dissection, beginning at its medial end. The vein is lifted up with a small vein retractor and its branches clamped, cut, and tied one by one as the dissection proceeds laterally. The mass of tissue between the vein and the chest wall is dissected downward and outward off the surface of the subscapular muscle, leaving the long thoracic nerve as the only structure crossing the medial part of the axilla in a longitudinal direction.

When the dissection of the tissues from the subscapular muscle reaches a point where the thoracodorsal nerve is encountered as it arches down from beneath the axillary vein to join the subscapular vessels, a decision has to be made whether to sacrifice or to preserve it. We have pointed out that this nerve, during the last 6 or 8 cm. of its course before it enters the latissimus muscle, lies among the lymph nodes of the scapular group. In our opinion it is unreasonably hazardous to dissect the nerve out from among these lymph nodes if it seems likely that they contain metastases. If palpation of the axilla has suggested lymph node involvement or if, in the course of the axillary dissection up to this point, there has been any gross evidence of axillary metastases, we sacrifice the thoracodorsal nerve forthwith. The paralysis of the latissimus which results, with weakness of abduction and internal rotation of the arm, is not a serious handicap.

If the nerve is preserved it is drawn medially and dissected away from the subscapular vessels.

The subscapular vessels themselves are regularly sacrificed in our technique. They are clamped, cut, and tied just beyond the point where the scapular circumflex branches are given off, usually 3 or 4 cm. from their origin.

The axillary vein having been cleared all of the way out to the point where it crosses the outer edge of the latissimus dorsi muscle, the mass of axillary tissues, now freed from all of its medial and cephalad connections, is dissected in a caudad direction down over the surface of the pyramidal muscle body formed by the subscapularis medially, and the teres major and the latissimus dorsi laterally. If the thoracodorsal nerve, as well as the subscapular vessels, has been sacrificed this part of the dissection is quickly done.

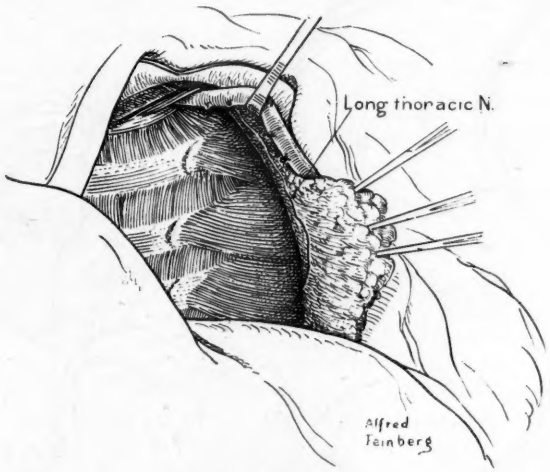

Fig. 20.—Dissecting the medial aspect of the axilla.

The final step in the axillary dissection is the excision of the specimen from along the groove between the chest wall and the latissimus dorsi, its only remaining attachment. This is carried out along a longitudinal plane and from the chest wall toward the latissimus as shown by the arrows in Fig. 21. More ventrally the dissection along this plane had included the removal of the fascia over the serratus, but when, in this final stage, the dissection reaches the level of the long thoracic nerve as it lies upon the serratus fascia, the operator must take care to dissect more superficially in order not to damage the nerve.

When the medial aspect of the latissimus dorsi is reached the plane of dissection is turned laterally. A little outward traction on the specimen as it lies on the table at the patient's side enables the operator to roll, so to speak, the remaining tissues laterally over the latissimus dorsi. In this process the branches of the subscapular vessels which turn medially to supply the chest wall opposite the apex of the subscapular and teres major muscle body, as well as those which enter the latissimus itself, are isolated, clamped, and ligated. These vessels are of considerable size, and the region has been aptly called the

"bloody angle" of radical mastectomy. With the technique which we have described here, however, there is no need of any hemorrhage, for the surgeon's access is good and the vessels easily identified.

To complete the dissection, the specimen is cut free from the edge of the latissimus dorsi. The operative field, as it appears at the end of the dissection, is shown in Fig. 22.

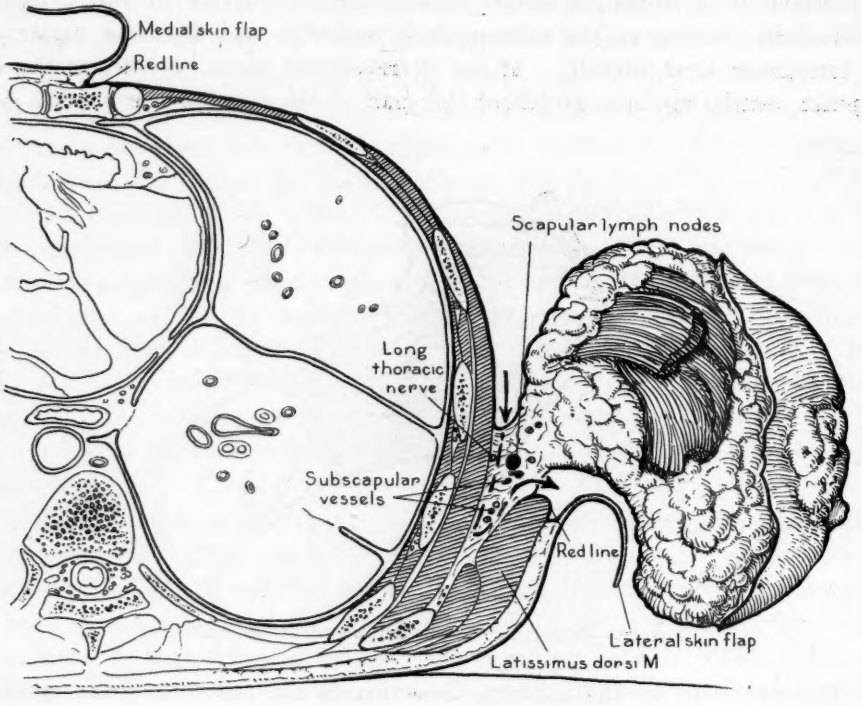

Fig. 21.—The final step in the dissection.

STEP 8. THE CLOSURE OF THE WOUND

We carefully inspect the whole extent of the wound, to be sure that it is dry, for if it is to be closed without draining, as is our custom, hemostasis must be meticulous.

The skin flaps are then replaced on the chest wall and sutured together at the upper and lower ends of the wound with interrupted sutures of B silk on fine straight needles. The suturing is carried only as far as the flaps will come together without excessive tension. By this we mean a degree of tension which will cause necrosis. Our flaps are so thin that the amount of tension required to damage them is not great. The operator has to learn by experience what is safe. Blanching of the skin of the flap beyond the suture is the best sign that too much tension has been used.

A defect of varying size remains. This is rarely less than 12 cm. in diameter, and is often considerably larger. The edges of the skin flaps around

the defect are sutured down to the chest wall with interrupted sutures of silk, their ends being left one inch long and laid out on the surface of the flaps so that they can be easily picked up from beneath the overlapping edges of the skin graft when it is time to remove them (Fig. 23). In suturing the edge of the lateral flap to the chest wall to make the required even curve, it is often necessary to pucker the edge a little between the sutures, but this straightens out very well in the healing process.

The defect is covered with a Thiersch graft, which is usually taken from the outer surface of the thigh. Since it is quicker to cut the graft by hand than with the dermatome we usually use the former method. If the operator is unable to cut a large enough graft with the Blair knife to cover the defect in one piece he had best use the dermatome. The graft should overlap the edges of the flaps slightly, so that a continuous suture of silk can be placed through it around its edge, fastening it securely to the underlying flap edges. It is then covered with a single layer of xeroform waxed gauze.

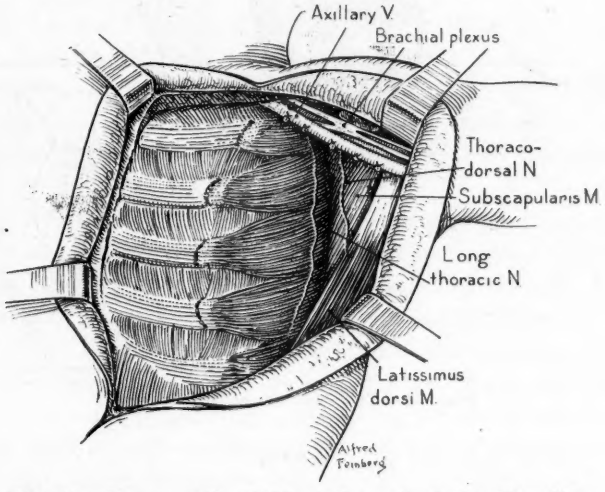

Fig. 22.—The operative field at the end of the dissection.

No drain is used. We have found that if hemostasis is meticulous none is required. In perhaps one-fifth of our patients a small accumulation of serum beneath the axillary end of the lateral flap results. One or two aspirations of the serum are required, but we regard this as a lesser evil than drainage. The use of a drain favors infection in some degree at least, for it is a foreign body in the wound, and it provides a channel of communication between the wound and the outer world.

STEP 9. THE DRESSING

The application of the operative dressing is as important as the dissection itself, and must not be left to an assistant who is unfamiliar with its details. Our aim is to apply pressure which will obliterate the dead space in the axilla, hold the graft in contact with the chest wall, and immobilize the arm, shoulder,

and chest as much as possible for forty-eight hours. We use fluffed gauze to obtain the pressure, packing it gently into the axilla in between the chest wall and the arm, and over the chest wall, until the surface is flat. We have tried other materials for this purpose but none equals fluffed gauze. The forearm is laid across the upper abdomen, encased in a thick layer of cotton. Two six-inch ACE bandages are then applied around the chest and arm, and securely fastened with safety pins.

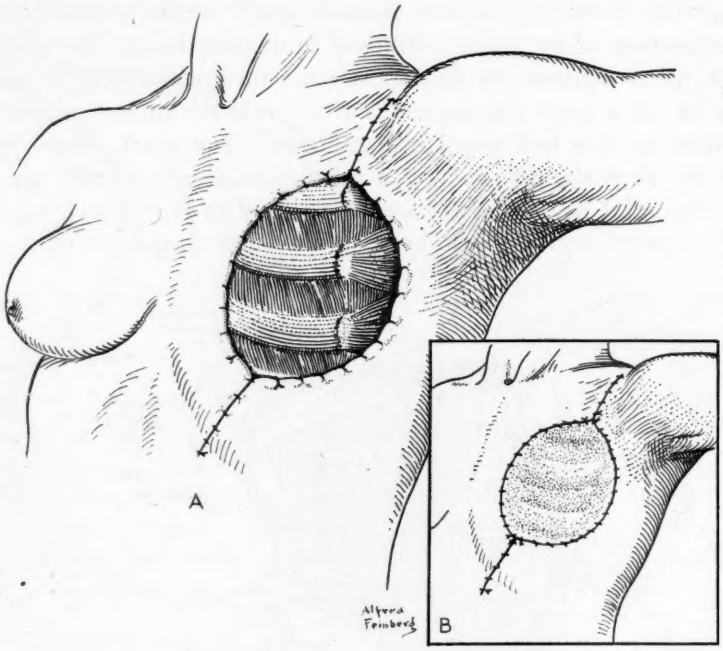

Fig. 23.—The closure of the wound.

SHOCK

The experienced operator, working steadily and rapidly, can complete this operation in five hours. A less experienced surgeon will require an additional hour. Unless precautions are taken to avoid it, shock will usually develop after this length of time. The most important of these precautions is careful hemostasis. After a little familiarity with the special anatomy of the region the surgeon can identify and clamp almost all of the vessels before cutting them. We use silk throughout the operation and it is our impression that its use favors good hemostasis. As compared with catgut, silk is a finer and more pliable ligature material, and the surgeon using it develops a sense of precision and delicacy which enables him to tie small vessels accurately.

Gentle handling of the tissues is also important. The late George Crile put it well many years ago when he classified surgeons as the carnivorous type who stretch, tear, and crush the tissues, and the herbivorous type who dissect gently.

In operations like the one we have been describing where a large area is denuded, drying of the tissues must be guarded against for it, too, causes shock. We keep all of the wound, except the small area in which we are dissecting, covered with moist towels or compresses. It is not possible to indicate in the drawings, which we have included to illustrate the steps of our operation, the degree to which we keep the tissues covered, but we hope the reader will understand that it is our constant care.

It is usually desirable to guard against the development of shock by giving an intravenous infusion of normal saline solution during the last part of the operation. One thousand cubic centimeters, run in slowly, is ordinarily sufficient. If shock nevertheless develops, we give whole blood promptly, but it is not often that it is needed. The blood pressure, after its initial fall due to the depressive effect of the avertin, usually maintains a remarkably even level if the precautions which we have described are followed.

THE AFTERCARE

Rest for the wound and early resumption of fluid and food intake are the immediate objectives of the aftercare. Rest for a wound of the chest wall can be only relative, of course, because of the respiratory movement, but it is of benefit to keep the patient on her back without turning for the first forty-eight hours. This position is tedious, but since we use morphine generously during this period, patients usually tolerate it.

At the end of forty-eight hours we remove the ACE bandages and the fluffed gauze, but we do not disturb the xeroform gauze covering the skin graft. There is no longer any need of a pressure dressing and we cover the wound merely with several layers of gauze fastened with a frame of adhesive around its edges.

On the sixth or seventh day we take down the dressing completely for the first time, removing the sutures around the graft and trimming its overlapping edge. It is wise to leave in place a few of the sutures which fix the flaps to the chest wall, as well as alternate ones along the suture line of the flaps, for a few additional days.

Our patients are ordinarily out of bed on the seventh postoperative day and home on the fourteenth day. The donor area on the thigh, also covered originally with xeroform gauze, is not ordinarily dressed until the day of discharge, when it will be found to be healed.

Some special attention must be given to arm function. After the compression dressing has been removed and the arm freed forty-eight hours postoperatively, we urge the patient to use her arm for all its usual functions, such as eating and writing, except those which require marked abduction. By the seventh or eighth day postoperatively the axillary flap is usually well adhered to the chest wall and from that time on we urge the patient to increase abduction gradually. During the month that follows, almost the full range of arm motion should be regained. In achieving it, patients have to bear some discomfort, but this is not greater than most will tolerate. The objection occasionally raised that the Halsted operation cripples the arm is incorrect. Pa-

tients who cooperate are eventually able to use the arm for everything from scrubbing floors to playing golf. Fig. 24 shows the absence of any constricting band across the axilla in one of our own patients.

Edema of the arm has always been a hazard of radical mastectomy. We believe that its cause is probably a low-grade sclerosing infection in the axilla. Careful obliteration of the axillary dead space, thus minimizing the accumulation of serum and the opportunity for infection, is the best preventive measure if this theory is correct. Our own experience, at least, confirms it, for we have little trouble with edema. A slight degree has developed occasionally, but marked edema has been rare.

Fig. 24.—Arm motion following radical mastectomy.

The Halsted radical mastectomy has not achieved much popularity in this country, or indeed anywhere in the world, during the half century since the operation was first done. Its performance demands patience and fortitude, but we trust that surgeons do not avoid it on this account. It is our hope that the operation has not been popular because it has been but little known, and our purpose in describing it here in detail has been to interest surgeons in it. Properly performed, the operation is safe, and gives a satisfactory functional result. And its truly radical character as compared with the usual so-called radical mastectomy gives an edge of advantage over that formidable opponent, mammary carcinoma.

REFERENCES

1. Meyer, Willy: Cancer of the Breast, Surg., Gynec. & Obst. 24: 553-577, 1917.
2. Cooper, William A.: The History of the Radical Mastectomy, Ann. M. Hist. 3: 36-54, 1941.
3. Haagensen, C. D., and Stout, A. P.: Carcinoma of the Breast. Criteria of Operability, Ann. Surg. 118: 1, 1943.

4. Handley, W. Sampson: Cancer of the Breast and Its Operative Treatment, London, 1906, John Murray.
5. Halsted, William Stewart: Surgical Papers, Johns Hopkins Hosp. Rep. 4: 297-350, 1894-1895.
6. Eisler, Paul: Die Muskeln des Stammes, in Handbuch der Anatomie des Menschen II/2/1, Jena, 1912, Gustav Fischer, pp. 481-506.
7. Leaf, Cecil H.: Cancer of the Breast: Clinically Considered, London, 1912, Constable & Co., Ltd.
8. Bartels, Paul: Das Lymphgefässsystem in Handbuch der Anatomie des Menschen III/4, Jena, 1909, Gustav Fischer, p. 166.
9. Rouvière, H.: Anatomie des Lymphatiques de l'Homme, Paris, 1932, Masson & Cie, p. 202.
10. Rouvière, H., translated by M. J. Tobias: Anatomy of the Human Lymphatic System, Ann Arbor, Michigan, 1938, Edwards Brothers, Inc.
11. Oelsner, Judwig: Anatomischer Untersuchungen ueber die Lymphwege der Brust mit Bezug auf die Ausbreitung des Mammacarcinoms, Arch. f. klin. Chir. 64: 158, 1901.
12. Mornard, Pierre: Etude anatomique des lymphatiques de la mamelle, au point de vue de l'extension lymphatique des cancers, Rev. de Chir. 51: 462, 1916.
13. Eisler, Paul: Die Muskeln des Stammes in Handbuch der Anatomie des Menschen II/2/1, Jena, 1912, Gustav Fischer, p. 505.

THE TREATMENT OF INOPERABLE CARCINOMA OF THE BREAST WITH IRRADIATION

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MOST experienced radiotherapists are enthusiastic about the good results obtained with radical surgery in early cancer of the breast, but less than one-fourth of the patients entering cancer clinics today can hope for a surgical cure. This statement is well borne out by the carefully compiled statistics of Haagensen and Stout[1] who recently reported a series of 1,040 patients with mammary cancer seen at the Presbyterian Hospital in New York from 1915 to 1934. Of this group 640 were treated by radical mastectomy and 231, or 22.2 per cent of the total number, were classed as five-year clinical cures. This means that 809, or 77.8 per cent of the total number, finally succumbed to the disease and required some form of palliative therapy during the final years of their lives.

Daland[2] has shown that the average duration of life in untreated cancer of the breast is 40.5 months from the time of observation of the first symptoms, while 40 per cent of the patients are alive at the end of three years, 22 per cent at the end of five years, 9 per cent at the end of seven years, and 5 per cent at the end of ten years. These figures indicate that in actual practice the effort expended in the care of incurable mammary cancer completely overshadows the purely surgical phase of the subject and yet the surgeons have written so prolifically about their side of the picture that the general physician who loses all interest when surgery fails is hardly to be blamed for his attitude.

Certainly more should be written about the palliative treatment of cancer, a field in which the radiologist now plays a major role. Pack[3] has recently criticized the existent attitude of both the laity and the profession toward this important subject. The properly treated patient with incurable cancer of the breast often has a life expectancy of from three to ten years, a great portion of which may be lived in comfort. As Pack pointed out, the diagnosis of such incurable diseases as arteriosclerosis, chronic nephritis, diabetes mellitus, and coronary disease is accepted with equanimity, fortitude, and optimism by most patients, whereas the term cancer tends to induce deep mental depression in both the patient and the attending physician.

SELECTION OF CASES

Tumor clinics have found it extremely difficult to formulate plans of procedure designed to give each cancer patient the best available treatment. Although radical mastectomies have been done for more than fifty years, scientifically sound indications for the operation have crystallized very slowly. Every radiologist who has taken care of postoperative mammary cancer has been impressed with the obvious harm done by surgery in certain instances and Haagen-

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sen and Stout have recently produced definite confirmation of this impression. Their studies have produced data which now make it possible for the physician to decide whether a patient with carcinoma of the breast should be subjected to surgery or receive only palliative therapy. They stated, "Women of all age groups who are in good enough general condition to run the risk of major surgery should be treated by radical mastectomy except as follows: (1) when the carcinoma is one which developed during pregnancy or lactation; (2) when extensive edema of the skin over the breast is present; (3) when satellite nodules are present in the skin over the breast; (4) when intercostal or parasternal tumor nodules are present; (5) when there is edema of the arm; (6) when proved supraclavicular metastases are present; (7) when the carcinoma is the inflammatory type; (8) when distant metastases are demonstrated; (9) when any two or more of the following signs of locally advanced carcinoma are present: (a) ulceration of the skin; (b) edema of the skin of limited extent (less than one-third of the skin over the breast involved); (c) fixation of the tumor to the chest wall; (d) axillary lymph nodes measuring 2.5 cm. or more in transverse diameter and proved to contain metastases by biopsy; (e) fixation of axillary lymph nodes to the skin or the deep structures of the axilla and proved to contain metastases by biopsy."

METHODS OF TREATMENT

In 1932 Adair[4] summarized the various procedures used successfully in the palliative care of advanced cancer of the breast. In addition to irradiation therapy he listed palliative surgery for the removal of sloughing, necrotic tissue, and local recurrences; electrocoagulation for the removal of small skin recurrences; medication for anemia, anorexia, sleep, relief of pain, and bone repair; special surgical procedures for the relief of lymphedema of the arm; plaster of Paris jackets and casts for fractures, and cordotomy for the relief of severe pain. In addition to all of these things the cancer patient derives an unbelievable amount of good from a cheerful and hopeful attitude assumed by her physician whether he be a surgeon or a radiologist. The improvement in morale becomes apparent early when a woman who has been told that she has a hopeless condition enters a clinic where numerous things are done for her by a physician who inspires confidence.

The radiologist has a number of helpful methods at his command. Although some clinics use radon seeds for interstitial therapy, we favor the weak radium needles advocated by Keynes.[5] These needles produce a minimum of sloughing and fibrosis and their careful use will often completely eradicate both primary and secondary malignant tumors in and about the breast. Although we do not believe that they should be given preference over radical surgery when it can be done, they become very useful in those cases in which the more radical procedures are contraindicated.

In our clinic, needles having active lengths of 2.0 and 4.0 cm. and wall thicknesses of 0.6 mm. of platinum are used. All of the needles contain approximately 0.6 mg. of radium per cm. of active length and they are placed approximately 1.0 cm. apart in layers within or beneath the tumor to be treated for a

period of seven days. The methods of implanting the needles and calculating dosage have been described in previous articles.[6, 7] Some have advocated the use of large numbers of these needles applied externally to the chest wall by means of a radioactive jacket, but this method is uneconomical and has been followed by rib damage in enough cases to render its value somewhat doubtful.

Radiotherapists have attempted actually to cure malignant tumors of the breast with x-rays for many years, using one technical variation after another. Although these tumors may partially or completely disappear, they are seldom permanently controlled when the doses used are safe for the normal tissues. Unfortunately, the fat overlying and incorporated in the breast and the pulmonary structures lying immediately beneath it are seriously damaged by curative doses, particularly when areas large enough to include the original growth and its lymphatic extensions are irradiated. The alveolar structures in the lungs are especially sensitive to x-rays and the type of damage produced has been carefully studied by Groover, Christie, and Merritt,[8] McIntosh and Spitz,[9] Freid and Goldberg,[10] Warren and Spencer,[11] Jacobson,[12] and Leach, Farrow, Foote, and Wawro.[13] Even with a divided dose technique which tends to spare normal structures, Leach, Farrow, Foote, and Wawro observed many cases of pulmonary fibrosis in which the lung received approximately 5.0 T.E.D., and in some instances the irradiation reaching the lung amounted to only 2.5 T.E.D. Since 5.0 T.E.D. is well below the curative dose the limiting factor of pulmonary fibrosis becomes evident.

In treating breast tumors the x-ray beams are always directed tangentially to the chest wall in an effort to diminish lung damage but efficient irradiation of the deep lymphatics of the chest wall and axilla must include some of the pulmonary structures.

A patient can survive even when an entire lung is fibrosed, but elevation of the dosage above safe limits for the pulmonary structures frequently produces a radiation osteitis in the ribs and pathologic fractures may occur. Paul and Pohle[14] have recently described fifteen such cases.

Pulmonary fibrosis, severe skin reactions, and irradiation osteitis produce very unpleasant symptoms. Palliative x-ray therapy should, therefore, be given with techniques which reduce these sequelae to a minimum.

In the beginning single massive doses of x-rays were administered to each area treated, and moderate voltage and filtration were used in an effort to deliver a relatively large dose to the chest wall and breast and a relatively small dose to the underlying lung. Large doses were delivered to breast tumors by crossfiring them through a number of areas. This method is still used at the Mayo Clinic, and MacCarty and Leddy[15] report satisfactory regression of ulcerating carcinoma of the breast treated through four to six sectors at one sitting. The factors used are: 130 kv.; a target skin distance of 40 cm.; a tube current of 6.0 Ma.; a filter of 6.0 mm. of aluminum, and a dose per area of 500 to 600 roentgens. (All x-ray doses noted in this paper are given in roentgens measured in air.)

Many metastatic lesions cannot be efficiently crossfired and a single dose of 600 roentgens given through one skin area is not large enough to produce the

best results. In 1932 Coutard[16] first reported the French divided dose method in the American literature. He showed that doses large enough to damage cancer cells severely could be given safely through a single area when only a fraction of the total dose was given each day. Coutard originally treated carcinoma of the larynx and pharynx situated several centimeters below the skin surface and it seemed logical to apply his technique to cancer of the breast located at a similar depth. In 1933 such a plan was adopted at the Memorial Hospital in New York and in 1935 some of the results were reported by Adair.[17] He observed a complete microscopic disappearance of carcinoma in 33 per cent of the breasts in which 1,800 roentgens were applied to each of two portals laid out so as to crossfire the tumor, and a similar result in 22 per cent of the metastatic axillary lymph nodes crossfired in the same manner through three portals. This work was done with 200 kv. equipment and each area received not more than 300 roentgens per day. Adair did not use more than 1,800 roentgens per area because his work was done on patients with operable cancer and he wished to keep the normal tissues in good condition for operation.

Patients with inoperable cancer can be given larger doses and in our clinic 15 cm. portals are treated with 2,100 to 2,400 roentgens at the rate of 300 roentgens daily. Smaller areas may be treated even more intensively with safety.

The value of castration in the care of advanced mammary cancer was first established in 1896 when Beatson[18] reported improvement following surgical removal of the ovaries in three cases. Other surgeons have reported improvement in approximately 25 per cent of the patients treated by surgical castration and Foveau de Courmelles[19] described the first good results obtained with irradiation castration in 1909. The method is most useful when bone metastases are present and should always be tried when a patient with inoperable cancer has not reached the menopause. In our clinic the artificial menopause is produced by applying 600 roentgens to each of four 15 cm. portals, treating one area per day for four successive days. Two areas are laid out over the front and two over the back of the pelvis. The factors are: 200 kv., a target skin distance of 50 cm., a tube current of 25 Ma., and a filter of 0.5 mm. of copper and 1.0 mm. of aluminum. The menopause should be fully established about six weeks after the completion of this therapy.

IRRADIATION SICKNESS

The administration of large doses of x-rays usually produces a syndrome characterized by anorexia, malaise, nausea, and vomiting. The severity of the symptoms depends upon the size of the daily dose, the size of the area treated, and particularly upon the portion of the body irradiated. The most severe reactions are produced by treatment of the upper abdomen. Thirteen theories covering the mechanism producing this condition are listed in a previous article,[20] but the exact cause of the symptom complex is still poorly understood.

Drugs capable of depressing the vomiting center are very helpful in relieving the nausea and vomiting. In our early work we used chloral hydrate and sodium bromide with some success, but in more recent years the barbit-

urates have proved more valuable. Nembutal has been recommended by Richards and Peters[21] and Popp,[22] and a 3 gr. nembutal suppository will usually produce marked relief. The intravenous injection of salt solution and glucose has also produced amelioration of the symptoms and the administration of one or two liters of 5 per cent glucose in a normal saline solution should be used when nausea and vomiting persist.

Many attempts have been made to perfect a preventive form of medication which might be given the ambulatory patient before and during the period of irradiation. In 1933 Dietel[23] reported good results obtained with liver extract and Webster[24] and Young[25] substantiated his findings. These reports pointed to vitamin imbalance as a possible underlying cause of treatment sickness and a series of experiments[26] carried out at the Baylor Medical School in 1937 seemed to indicate that animals could be partially protected against roentgen intoxication by vitamin B_1. After trying various combinations it is now our belief that the entire B complex gives some protection against the milder forms of irradiation sickness and that it is better than any one of its component parts.

Before a long series of x-ray treatments is started the patient is asked to take a capsule after each meal containing 1 mg. of thiamine chloride, 0.333 mg. of riboflavin, 200 μg. of pyridoxine hydrochloride, 2.0 mg. of nicotinic acid, and 250 μg. of pantothenic acid. When possible, a daily intramuscular injection of 1.0 c.c. of liver extract containing 2.0 U.S.P. units is also given. If the patient's condition is poor or if nausea and vomiting appear, the oral vitamin therapy is replaced by a daily intravenous injection of 2.0 c.c. of a solution containing 10 mg. of thiamine chloride, 4.0 mg. of riboflavin, 150 mg. of nicotinamide, 10 mg. of pyridoxine hydrochloride, and 5 mg. of pantothenic acid. This type of medication not only offsets the effect of the irradiation but it tends to improve the patient's appetite and general health as well.

The successful use of large doses of pyridoxine hydrochloride in controlling the nausea and vomiting of pregnancy was reported by Willis, Winn, Morris, Newsom, and Massey[27] in 1942. This work, done at the Baylor Medical School, has been subtantiated by Weinstein, Mitchell, and Sustendal[28] and suggests a specific effect of vitamin B_6 on nausea of toxic origin. We hope to have data in the near future on the use of this drug in the treatment of irradiation sickness.

LESIONS TREATED

Large Tumors in the Breast in Incurable Cases.—When large masses of malignant tissue have become necrotic and are producing a foul odor, surgical resection offers quick symptomatic relief. However, these large tumors often show marked shrinkage following radiation. When an infected ulcer has appeared in a large tumor the use of activated zinc peroxide paste for several days prior to irradiation is a helpful procedure. The multiple single dose method given through four to six sectors is quite satisfactory but most radiologists prefer to crossfire the tumor through two or three portals, using a

divided-dose tangential technique with 200 kv. equipment. Each portal may be given 2,100 to 2,400 roentgens at the rate of 300 roentgens per day to each area. This type of therapy produces a marked skin erythema in eight to ten days followed by desquamation and tanning. When this reaction is at its height the patient complains of some burning and itching and obtains much relief from the free use of a wash containing 1.0 gr. of phenol, 2.0 dr. of glycerine, 4.0 dr. of zinc oxide, and 6.0 ounces of limewater. In certain locations portions of the treated skin may be temporarily denuded. When the skin surface is lost the wash should be replaced by a soothing ointment. Boric acid or nupercainal ointment usually gives relief. Tumor regression becomes apparent in about three weeks after the treatment is finished and may continue for another three to six weeks.

Involvement of the Skin.—This complication may manifest itself as a puckering of the skin, a reddened thickened-area nodule formation, or cancer en cuirasse. As O'Brien[29] has pointed out, the appearance of skin metastases is almost always a very bad prognostic sign and a cure is rarely obtained. Occasionally radical treatment of a small single recurrent nodule is successful but the common surgical practice of removing one recurrence after another from the skin and subcutaneous tissues has little to commend it. Adair[30] stated that since "surgery fails in a larger proportion than heavy irradiation, it is best to treat a definite region of recurrence with a sufficiently large portal to more than cover it, employing about 200 r to 250 r daily, up to approximately 4,000 r total." Although he advocated a voltage of 200 kv., Fried and Goldberg[31] used a somewhat lower dosage with low or intermediate voltage in an effort to spare the pulmonary tissues. We prefer implanted low intensity radium needles for such lesions because a curative dose can be safely administered without damaging the intrathoracic structures.

When multiple nodules or cancer en cuirasse appear, no type of treatment will cure the patient and only palliative therapy is indicated. Prolonged improvement often follows the use of divided doses of x-rays generated at 200 kv. The entire anterior chest wall should be divided into 15 cm. squares, 1,800 to 2,100 roentgens being administered to each at the rate of 300 roentgens per day. This therapy may be repeated after six to eight months, if necessary, and the skin lesions can in most instances be fairly well controlled until internal metastases appear.

Parasternal masses which are attached to the chest wall and may or may not ulcerate through the skin may be completely eradicated with irradiation therapy. Adair reported ten such cases successfully treated with 15,000 mc. hr., given by means of a radium pack and followed by a single massive dose of high voltage x-rays. We use weak radium needles for these lesions and all others where it is desirable to give a large dose to an accessible tumor.

Metastases in Axillary Lymph Nodes.—Enlarged axillary glands containing carcinoma are found following operation when the nodes apparently were too deep for complete extirpation and in advanced cases which are beyond

surgical aid. A swollen arm on the affected side is often produced by the pressure of such glands on the return circulation. However, in some cases the lymphedema results from operative procedures or from the fibrosis produced by intensive irradiation.

For some reason which is not understood, cancer cells growing in lymph nodes are more resistant to irradiation therapy than the malignant cells found in the primary tumor. Axillary fat stands heavy irradiation very poorly and although a combination of interstitial radium and a crossfire x-ray technique sometimes produces complete regression of cancer in axillary nodes, the resulting reaction is not justified in incurable cases. When implanted radium needles or radon seeds are used, great care must be exercised to space the sources so that an excessive dose will not reach the brachial plexus. Such a mishap produces intractable excruciating constant pain which is to be avoided even though the response to treatment is satisfactory.

Duffy and Lucas[32] have estimated the dosage delivered to the depths of the axilla with external x-ray therapy administered through two, three, four, and five portals. With 200 kv. equipment and three portals, the dose reaching the deeper glands amounts to 200 per cent of that given each area. Anterior and posterior portals measure 10 by 10 cm. and a third area on top of the shoulder measures 10 by 8 cm. When each portal receives a total of 2,100 roentgens given by the divided-dose technique, the palliative results are usually good and in some instances similar doses given to 15 by 15 cm. areas laid out over the front and back of the axilla suffice.

Metastases in Supraclavicular Lymph Nodes.—Careful palpation may reveal small metastatic nodes just behind the inner end of the clavicle or just behind the mid-portion of the bone. Since this finding renders the patient incurable its detection is most important. In later stages of the disease multiple glands appear extending from the mastoid to the clavicle. Deep-seated nodes below the mastoid may produce pain about the ear and edema of the face.

Carcinomatous invasion of the brachial plexus constitutes one of the most difficult problems encountered. Pain in the arm is so intense that morphine does not give relief and the muscles of the hand show marked atrophy. The patient is thoroughly exhausted from loss of sleep and the condition is indeed pitiful. Irradiation produces no improvement and a high cordotomy offers the only hope of relief.

Although Adair has reported the control of isolated supraclavicular nodes with very heroic external irradiation, his results necessitated severe damage to the skin, subcutaneous tissues, and clavicle. In our experience single nodes are best treated with implanted radium needles of the Keynes type. Although the skin over the implanted area develops atrophy and telangiectasia, the damaged region is localized and produces no untoward symptoms. Supraclavicular nodes have remained quiescent for three to six years following this procedure.

Larger areas must be treated with external irradiation and the neck does not lend itself well to a crossfire technique. For this reason the divided-dose

method must be used over single portals. The skin of the base of the neck is easily damaged with x-rays and the total dose used rarely exceeds 2,100 roentgens. When this type of therapy is directed toward the midline, a rather severe reaction is produced in the mucosa of the esophagus. In six or seven days after the treatment is finished the patient complains of soreness and difficulty in swallowing, but these symptoms subside after seven or eight days and no permanent injury results. It is sometimes necessary to use only soft and liquid food during the reaction stage and cold foods such as ice cream are well tolerated. Acetyl salicylic acid or one of the nupercaine preparations may be dissolved in the mouth and swallowed slowly before each meal for relief of discomfort.

Skeletal Metastases.—Osseous metastases from mammary cancer may appear in practically every bone in the skeleton. Lenz and Freid[33] have made a painstaking study of eighty-one such cases. In only six did roentgenographic or clinical evidence of other metastases precede skeletal invasion. The regions most frequently involved were the pelvis, spine, and femurs. The first symptoms were usually pain and pressure tenderness and in 75 per cent of these patients the examiner's attention was drawn to the bone metastases because of the complaint of localized pain. In nine cases the complaint of pain preceded the roentgenographic demonstration of the lesions by one-half to twelve months. Pathologic fracture was observed in twenty-one cases and this complication often occurred before the skeletal invasion became widespread.

In the roentgenogram two types of metastases are observed. One, which is likely to become widespread, is characterized by a diffuse moth-eaten appearance, while in the other localized areas of complete bone destruction with sharply defined margins are seen. Many involved vertebral bodies collapse early producing various stages of kyphosis and in some instances a transverse myelitis from pressure on the spinal cord.

The radiotherapist dealing with this complication is doubly blessed because he has at his command two methods of treatment capable of producing good results. It has been known for years that relatively small doses of x-rays delivered directly to bone metastases of mammary origin often relieve pain and may even produce a recalcification of the destroyed osseous structures. In 1931 Daland[34] reported striking improvement of generalized metastatic bone lesions in a patient subjected to x-ray castration and in 1933 similar results were obtained in our clinic. In 1936 Dresser[35] published a careful study of thirty women affilicted with skeletal metastases treated by x-ray castration alone. Of this group 43.3 per cent obtained relief of pain, 30 per cent showed regression of the lesions, and only 26.6 per cent showed no response to treatment. No improvement was observed following ovarian irradiation in any woman past the menopause. In 1936 we[36] reported a small series of cases in which the two methods were combined. In this experience very few patients who have not reached the menopause fail to obtain relief of pain from this plan of treatment. The patient first receives four massive doses of x-rays over the pelvis to produce an artificial menopause as previously described. Each metastatic

area is then crossfired through two or more 15 by 15 cm. portals, a dose of 600 roentgens being delivered to a single portal each day. This entire procedure can be carried out in a reasonable period of time even when multiple bone metastases are present. Relief of pain begins in two or three weeks after the series is finished and the maximum improvement appears in six to eight weeks. Most patients treated in this manner show a gain in weight of fifteen to twenty pounds and a general improvement in their appearance which is most striking. Unfortunately, the good results are not permanent but often last from one to three years. When bone pain reappears it can frequently be relieved a second time by repeating the local treatment.

Pathologic fractures are serious complications but their treatment is not necessarily hopeless. In many instances healing occurs when the treatment detailed here is combined with immobilization usually produced by means of a plaster cast. The x-ray therapy can be administered through windows cut in the cast and good union has appeared after the completion of the irradiation therapy. Adair and Freid and Goldberg advocated the use of the divided-dose technique in such cases and gave as much as 1,800 roentgens per area. Even compression fractures of vertebral bodies may show a good response if a plaster jacket can be put on early while traction is applied. Adair reported a return of sphincter control in both the rectum and bladder following such treatment used soon after the appearance of the symptoms of transverse myelitis.

Brain Metastases.—Intracranial metastases from carcinoma of the breast are relatively common in the last stages of the disease. Freid and Goldberg observed clinical evidence of such lesions in 20 per cent of 369 advanced cases. There was roentgenologic evidence of skull invasion in 61 per cent of this group, and direct extension from the metastases in the calvarium was demonstrated at autopsy in seven cases. Involvement of the pituitary occurred in four cases and of the pineal gland in two cases. Cerebral metastases found at post-mortem examination in five cases produced no symptoms during life. When the pituitary lesions were large enough to produce symptoms a typical diabetes insipidus was produced. The longest survival period after the discovery of cerebral involvement was thirty-two months. Localizing signs appeared without increased intracranial pressure in twenty-nine patients and were accompanied by such an increase in thirty patients. In nine the only symptoms were those of gradually increasing pressure. In our practice we have observed sixth nerve involvement as the first sign of brain invasion on so many occasions that we are constantly on the lookout for early strabismus.

Some neurological surgeons advocate the removal of brain lesions when other parts of the body are relatively free of metastases. However, the palliative results with irradiation are usually so good that this radical procedure seems unjustified. Relief of symptoms lasting from six months to two years has been observed and the treatment can oftentimes be successfully repeated.

It is our custom to crossfire the affected portion of the brain through two or three portals when localization is possible. In other cases the skull is treated

through four triangular portals covering the entire cranial vault. Each area receives a daily dose of 300 roentgens and a total dose of 1,800 roentgens, but only one area is treated per day. In some instances irradiation produces an increased intracranial pressure sufficient to require treatment but this complication is rarely troublesome. All of the hair falls out soon after the series is finished but it usually grows again after four to six months. In women an attempt is made to shield the top of the head so that the hair remaining in this region can be made to cover the bald spots, but in the more advanced cases this is not possible. Some patients wear wrap-around turbans with a small amount of hair attached to the edges so arranged as to conceal completely the absence of hair on the head.

Spinal Cord Metastases.—The symptoms of spinal cord pressure usually result from lesions growing from the vertebral bodies but occasionally the metastases are within the neural canal. In the series studied by Freid and Goldberg, invasion of the dura occurred in four cases and of the cord itself in two cases. Treatment of the type used for brain metastases is frequently effective if it is applied before permanent damage occurs. The rays are directed at the cord lesion through two to four portals depending upon its depth below the surface.

Intrathoracic Metastases.—Figures covering the incidence of intrathoracic metastases in patients dying of mammary cancer, published by different pathologists, show a marked variation but the discovery of this complication in 89 per cent of the post-mortem examinations reported by Freid and Goldberg indicates that a careful search will reveal some involvement of this region in almost every fatal case. The first extension may appear in the lungs, pleura, mediastinal nodes, heart, or pericardium, but as the disease progresses two or more of these structures usually are invaded. Combined invasion of the lungs, pleura, and mediastinal nodes is the commonest finding.

Since early lesions are often asymptomatic, an x-ray examination of the chest is one of the first steps in the examination of every patient. The smaller metastases, particularly those in lymph nodes, cannot be demonstrated and for that reason a routine roentgenogram of the chest should be made every two months.

The findings in the lung fields are of three varieties. Rounded, sharply defined, translucent areas of increased density are pathognomonic. However, in some cases the metastases appear as irregular dense areas with poorly defined borders of the type seen with disseminated tuberculosis, while in others a stranded invasive process extends into the lung fields from the hilus. Pleural involvement produces all of the roentgen-ray signs observed with pleurises of infectious origin and cannot be differentiated from them when the history is not available.

The earliest symptom is a nonproductive cough. As the intrathoracic lesions grow, dyspnea becomes a troublesome symptom and pain and tenderness in the chest usually indicate pleural invasion. Hoarseness from vocal cord paralysis and swelling of the neck secondary to pressure on the superior vena cava may follow enlargement of mediastinal lymph nodes.

On the whole, the treatment of intrathoracic lesions with roentgen rays is unsatisfactory. This is partially due to the fact that the patient is likely to be suffering from generalized carcinomatosis by the time intrathoracic metastases are well established. A localized pleurisy sometimes regresses after intensive irradiation therapy. However, we have seen pleurisy with effusion in cancer disappear without treatment and one cannot be certain that this complication is always of malignant origin. In the absence of pulmonary lesions, a crossfire technique applied to a pleurisy at one base is justified.

Generalized pulmonary metastases should never be irradiated because of the serious changes produced in the lungs by efficient dosage. Occasionally it seems worth while to treat a single nodule when the patient is in good condition and other metastases are not demonstrable. Moderate doses may also be directed at the mediastinum with some temporary success when pressure symptoms from enlarged glands produce severe distress.

As a rule better palliative results are obtained when irradiation of the thorax is omitted. The cough and discomfort are best controlled with mixtures containing codeine or morphine to which small amounts of one of the barbiturates are added. When pleural effusions appear paracentesis often relieves the resulting dyspnea.

Intra-abdominal Metastases.—Abdominal extension indicates a generalized dissemination of the disease in mammary carcinoma and no efficient method of retarding this dissemination is now available. Autopsy findings indicate that all of the viscera as well as the mesenteric and retroperitoneal lymph nodes and peritoneal surfaces may contain implants. The organs most commonly involved are the liver, adrenals, ovary, spleen, and kidney.

In most advanced cases the liver contains one or more metastatic nodules and shows some degree of enlargement. The nodules may compress the hepatic ducts and produce a marked jaundice. These changes give rise to a chronic indigestion characterized by epigastric fullness after eating, eructations, nausea, and vomiting. Persistent gastric symptoms in a patient with cancer of the breast always render the prognosis poor even though the liver is not palpable.

Constant abdominal pain may be due to a large, tender liver, marked ascites, or enlarged para-aortic and mesenteric lymph nodes. In some instances the pain resembles that produced by peptic ulcer or gastric cancer. The appearance of abdominal invasion is soon followed by weakness, cachexia, loss of weight, and a great variety of lesser symptoms.

Although some radiologists advocate irradiation therapy over the abdomen, particularly when the liver is enlarged, we believe that the questionable improvement obtained in no way offsets the objectionable symptoms of irradiation sickness which invariably follow this form of treatment. Patients with abdominal metastases are best handled by the internist who does an abdominal paracentesis when it is indicated and makes the victim's last days as comfortable as possible.

The following case histories illustrate some of the points covered in the paper and show that a patient may live for a number of years in relative comfort after the diagnosis of incurable mammary cancer is made.

CASE 1.—In 1933 a tumor was removed from the right breast of Mrs. F. C. B., who was then 35 years of age. The operation was done by her home physician who told her that the tumor was not malignant. In October, 1934, she visited a clinic in another city where a radical resection of the right breast was carried out. Adenocarcinoma, grade III, was found in multiple nodules in the breast and in two axillary lymph nodes. She received postoperative x-ray therapy over the chest and axilla in the same clinic. This treatment was repeated in 1935.

In 1937 she returned to the same clinic for surgical removal of a supraclavicular lymph node which contained adenocarcinoma. Following this operation x-ray therapy was given over both sides of the neck and the right axilla.

In February, 1941, the same physician removed a gland measuring 2.0 cm. in diameter from the left axilla and it also contained adenocarcinoma. This operation was followed by short series of x-ray treatments given in March, April, and July in 1941, and in November, 1942. At her last visit for x-ray therapy she complained of loss of vision. She could only detect light with the right eye but could see fairly well with the left eye. X-ray examinations of the skull, chest, and spine revealed no evidence of metastases.

She entered the clinic in January, 1943, just ten years after the onset of her illness complaining of headache, nausea, vomiting, a staggering gait, and complete loss of vision in the right eye. Examination revealed a small metastatic node in the left axilla but no other external evidence of carcinoma. Roentgenograms of the skull, chest, and spine revealed no evidence of metastases.

From Jan. 23, 1943, to Feb. 12, 1943, she received a daily dose of 315 roentgens delivered to three 10 by 15 cm. portals laid out over the occipital and both parietal regions. The areas were treated in rotation until each one received 1,890 roentgens and only one area was treated each day. The factors used were: 220 kv.; 20 Ma.; a target skin distance of 50 cm.; and a filter of 0.8 mm. of tin, 0.25 mm. of copper, and 1.0 mm. of aluminum.

She improved slowly and on March 30, 1943, was free of headache and vomiting and could walk without difficulty. The vision did not improve in the right eye. From March 30, 1943, to April 6, 1943, a total of 1,890 roentgens was administered to the left axilla using the same factors.

On Dec. 15, 1943, she returned complaining of pain in the right lumbar region, hip, and leg. Although x-ray examination showed no bone metastases, castration seemed to be indicated. On four successive days she was given 600 roentgens to each of four 15 by 15 cm. portals laid out over the front and back of the pelvis. The treatment factors were 200 kv., 25 Ma., a target skin distance of 50 cm., and a filter of 0.5 mm. of copper and 1.0 mm. of aluminum.

On Jan. 19, 1944, the pain in the lower back was much better but the patient complained of pain in the left shoulder and arm and weakness of the left hand. No evidence of metastases in the cervical spine was revealed by x-ray examination. However, single doses of 600 roentgens were given to 10 by 15 cm. portals over both sides of the neck and the anterior and posterior aspects of the left shoulder, using the same factors as at the last visit.

On March 15, 1944, the pain in the shoulder and arm was completely relieved and she had no new symptoms referable to the brain lesion except slight dimness of vision in the left eye. She also complained of some pain in the calf of the right leg. Single doses of 600 roentgens were delivered to 15 by 15 cm. portals over the anterior and posterior aspects of the right lumbar region and total doses of 1,800 roentgens were given to the lateral aspects of the skull through 15 by 15 cm. portals at the rate of 300 roentgens per day using the factors originally employed in treating the head.

When she left the hospital on March 30, 1944, she was free of pain and the vision in the left eye was improving.

Comment.—The progress of this patient illustrates the futility of repeated surgical removal of lymph nodes in an incurable case. The pain in the cervical

and lumbar regions may have been produced by bone metastases. In some instances pain appears months before bone changes can be demonstrated roentgenographically. This patient is rather remarkable in that she is alive with metastases and in fairly good condition eleven years after the appearance of an actively growing carcinoma of the breast.

CASE 2.—Mrs. P. P. entered the clinic in May, 1942, when she was 45 years of age. A hard tumor filled the outer half of the right breast and the overlying skin had an orange-peel appearance. Several small glands were felt high in the right axilla and two similar nodes measuring 1.0 cm. in diameter were felt above the mid-portion of the right clavicle. Roentgenographic examination revealed no evidence of intrathoracic metastases. A clinical diagnosis of inoperable carcinoma of the breast was made without microscopic confirmation.

X-ray therapy was administered over three areas. The breast was crossfired through two 15 by 20 cm. portals. The lateral portal included the axilla. A 15 by 15 cm. portal included the right neck above the clavicle. Daily treatments of 300 roentgens were given to single areas in rotation until each one had received a total of 2,100 roentgens. The treatment factors were 200 kv., 15 Ma., a target skin distance of 50 cm., and a filter of 0.4 mm. of tin, 0.25 mm. of copper, and 1.0 mm. of aluminum.

When the patient returned six weeks later the tumor in the breast was much smaller, the axillary nodes were just palpable, and the supraclavicular nodes could not be felt. The treated areas showed a marked tan and some desquamation.

In September, 1942, she developed a hacking cough with discomfort in the right chest. A roentgenogram revealed a small pleural effusion at the right base. The chest was strapped and she was given sedatives but no irradiation was administered. She returned six weeks later entirely free of symptoms and a roentgenogram showed no evidence of the pleurisy which apparently had an infectious etiology. At that visit the right breast was still somewhat enlarged and a deep mass of fibrosis was felt at the site of the tumor.

In October, 1943, she discovered a movable subcutaneous nodule measuring 0.5 cm. in diameter on the inner aspect of the right arm just above the elbow. A single dose of 640 roentgens was given to a 15 by 15 cm. portal centered over the nodule. The treatment factors were 200 kv., 15 Ma., a target skin distance of 50 cm., and a filter of 0.5 mm. of copper and 1.0 mm. of aluminum. In January, 1944, the subcutaneous nodule had disappeared and she felt perfectly well. The findings in the breast were unchanged and no other evidence of metastases could be found.

Comment.—This patient, who undoubtedly had an inoperable carcinoma of the breast, has remained symptom free except for a short attack of pleurisy for two years with x-ray therapy alone. A positive diagnosis could have been made from a supraclavicular node and perhaps one should have been removed for biopsy. Irradiation would have received false credit for relieving a malignant pleurisy if it had been used when the pleural complication occurred.

CASE 3.—Mrs. S. R. entered the clinic in October, 1935, when she was 54 years of age. A physician in a small town had just removed a rather large tumor from the right axilla and a reliable pathologist reported it to be an adenocarcinoma, grade III. About nineteen months prior to this operation a portion of the right breast had been removed without an axillary dissection by the same physician. At the time of admission she was symptom free and no evidence of metastases could be made out either by palpation or x-ray examination.

She received 300 roentgens daily over a 15 by 15 cm. axillary port until 2,700 roentgens had been administered. The treatment factors were 220 kv., 20 Ma., a target skin distance of 50 cm., and a filter of 20 mm. of copper and 1.0 mm. of aluminum.

She did well until November, 1928, when she returned with a hard, flat tumor measuring 4.0 cm. in diameter in the mid-portion of the remainder of the right breast. The overlying skin had an orange-peel appearance. The tumor was crossfired through two 15 by 15 cm. portals at the rate of 300 roentgens per portal per day until each area had received 2,100 roentgens. The treatment factors were 220 kv., 20 Ma., a target skin distance of 50 cm., and a filter of 0.8 mm. of tin, 0.25 mm. of copper, and 1.0 mm. of aluminum.

The tumor in the right breast melted away but in May, 1939, the patient returned with a diffuse swelling of the left breast, the skin of which showed an orange-peel appearance, and a gland measuring 3.5 cm. in diameter in the left axilla. The left breast was crossfired through two 15 by 20 cm. portals. The lateral portal included the axilla and the dosage was exactly the same as that given to the right breast at the previous visit.

All evidence of the disease melted away and she remained well unil May, 1941, when she returned with a hard, fixed tumor measuring 2.5 cm. in diameter, growing from the left chest wall just below the inner end of the clavicle. Roentgenograms of the chest wall and lung fields showed no metastases. A dose of 2,100 roentgens was given to a 15 by 15 cm. portal centered over this tumor at the rate of 300 roentgens per day. The tumor disappeared and in June, 1942, a similar series of treatments was given over the right neck because a few enlarged glands had appeared in this region.

In September, 1942, she returned to the clinic looking ill for the first time and complaining of hoarseness and weakness. A roentgenogram of the chest revealed some widening of the aortic arch and a few questionable enlarged mediastinal glands. The tumor in the right breast had recurred and measured 5.0 cm. in diameter. Because of her rather poor condition only a short series of massive doses was given. Four 15 by 15 cm. portals laid out over the mediastinum received 600 roentgens on successive days and the breast tumor was crossfired through two areas of similar size with the same dosage.

In December, 1942, she wrote that she had received some benefit from the last treatment and was moving to another city where she would be under the care of another radiologist.

Comment.—It is unnecessary to point out the fact that this patient's life might have been saved by radical surgery at the time of the first operation. However, palliative therapy gave her seven years of relative comfort during most of which time she led a normal life.

CASE 4.—Mrs. T. L. F., 45 years of age, entered our clinic in December, 1940, because of a large, foul-smelling, painful mass which filled the left axilla. Three years previous to admission she had consulted a cancer "quack" who applied a caustic paste repeatedly to a tumor of the left breast for a period of four weeks. She stated that the treatment was extremely painful. However, after a period of four months the slough separated and the resulting wound healed, leaving a very large scar on the chest wall. About eighteen months later the tumor began to grow again and extended up into the axilla. Although she was again treated with caustic paste the new lesion did not improve.

At admission the axilla was filled with a black mass of necrotic tissue. When it was cut away a deep ulcer lined with bleeding, friable tissue and measuring 8.0 cm. in diameter was seen in the axillary fossa. Specimens of this tissue were reported as carcinoma simplex, grade IV. Roentgenograms of the chest revealed no evidence of metastases. The wound was packed with activated zinc peroxide for twenty-four hours and thoroughly cleansed with hydrogen peroxide. A group of fourteen long platinum radium needles, each containing 2.4 mg. of radium in 4.0 cm. of active length, were then inserted into the axilla in a conical pattern so as to surround the malignant ulcer and left in place for seven days.

At the end of six weeks she was much more comfortable and the ulcer was about one-half its former size. Its surface was clean and no definite evidence of malignant tissue could be seen. However, when she returned four months later the ulcer was still present

and active malignant tissue was found at its edges. She was then referred to a surgeon who found it possible to do a resection of the axillary tissues and scar on the chest wall. Healing was uneventful and this patient has remained well for three and one-half years since the date of admission.

Comment.—This unfortunate woman could undoubtedly have been cured by radical surgery done when the tumor first appeared. Certainly she could have been saved a great deal of suffering. In the opinion of our surgical consultant, an operation would have been hazardous when she was first seen, whereas it was carried out with ease after the wound was cleaned up with irradiation.

CASE 5.—Mrs. S. J., 43 years of age, entered the clinic on July 9, 1943, because of marked swelling and pain in the right arm. About two years previous to admission a radical resection of the right breast was done in a small town for a proved carcinoma and she was given some form of x-ray therapy for a period of four weeks in another city. One year later a number of recurrent skin nodules were removed surgically. They rapidly reappeared and the surgeon then removed a large portion of the involved skin and applied a graft. Soon afterward the arm began to swell.

At the time of admission an indurated mass of tumor tissue extended from the anterior right chest wall well up into the axilla and the right arm was markedly swollen so that its function was almost completely abolished. Three enlarged lymph nodes measuring 1.0 cm. in diameter were felt above the mid-portion of the right clavicle. Roentgenograms of the chest revealed no evidence of metastases. Portals measuring 15 by 15 cm. laid out over the anterior and posterior aspects of the right axilla and over the right side of the neck each received total doses of 2,100 roentgens at the rate of 300 roentgens per day. The treatments were given on successive days and only one area was treated each day. The treatment factors were 200 kv., 15 Ma., a target skin distance of 50 cm., and a filter of 0.4 mm. of tin, 1.0 mm. of copper, and 1.0 mm. of aluminum. Since this patient was still menstruating, a castration dose was then given through four portals using the method previously described.

She showed steady improvement and at the end of two months was free of pain and had gained ten pounds. At that time the swelling in the arm was much reduced. At the end of ten months the general condition was excellent. The arm was still slightly swollen but she could use it freely. A few small nodules could still be palpated in the right axilla and the supraclavicular nodes were just palpable.

Comment.—This case shows the futility of attempting to control multiple skin recurrences with radical surgery. It also illustrates the value of irradiation in the treatment of a swollen arm produced by malignant invasion of the axilla.

CASE 6.—Mrs. F. B., 36 years of age, entered the clinic in 1931 in a semihysterical state after being told by her physician that she had only two months to live and that she might break one of her bones at any time. A radical resection of the left breast had been done for carcinoma in 1929. About one and one-half years later she began to lose weight and to complain of indigestion and pain in the chest. She went to a large clinic where x-ray examination revealed metastases in two thoracic vertebrae, several ribs, one clavicle, and both scapulae.

At the time of admission she was moaning with pain. Both arms were locked about her legs which were drawn up under her chin and she could not be relaxed because of a firm conviction that letting her legs down might produce a fracture. After the administration of large doses of barbiturates she was finally straightened out in bed. Castration

doses of x-rays were given over the pelvis on four successive days and single massive doses were given over each portion of the skeleton in which metastases were demonstrated.

The large doses of morphine which she had been taking were rapidly reduced and at the end of three weeks this drug was completely withdrawn. She was told daily that the information obtained from her former physician was incorrect and that her outlook was good.

At the end of six weeks she was almost free of pain, was able to sit up and was complaining of hot flashes. At the end of seven months she had gained a total of forty-two pounds and was able to lead a normal life. She attended social functions in the evenings and looked unusually well. Roentgenograms of the skeleton showed a recalcification of most of the metastatic areas.

At fourteen months single massive doses of x-rays were given over several tender areas in the thorax and lumbar spine. At sixteen months she revisited her original physician who discovered some asymptomatic metastases in the skull. She was much upset when her attention was focused on these lesions and it was necessary to do a complete epilation to restore her mental equilibrium. At two years pain appeared in the left chest and a moderate amount of bloody fluid was aspirated from the pleural cavity. Roentgenograms revealed a soft tissue mass measuring 3.5 cm. in diameter at the periphery of the lower left lung field. No x-ray therapy was given over this region and the pleural process did not progress. At two years and eight months rather severe pain appeared in the lower lumbar region. It was partially relieved by single massive doses of x-rays but she began to lose weight and complained of weakness. At three years and two months from the time of admission she died with multiple metastases in the liver and lungs.

Comment.—In our opinion this patient's physician erred in telling her of the seriousness of her condition and in giving her large doses of morphine as her only form of treatment. If x-ray therapy had been started immediately she could have been spared much mental suffering. It is our custom to tell such patients that they are suffering from a form of arthritis which can be treated with x-rays. Since some forms of arthritis are now treated successfully with irradiation many of our patients obtain relief without realizing that a serious complication has appeared.

SUMMARY

With the methods of treatment now available more than 75 per cent of all patients with cancer of the breast applying for treatment are incurable and must receive some form of palliative therapy.

Criteria are now available which make it possible to decide whether any given patient should receive radical surgery or only irradiation therapy and other palliative measures.

The care of patients with incurable mammary cancer has become rather complex but the intelligent use of irradiation therapy enables many of them to live three or more years in relative comfort.

REFERENCES

1. Haagensen, C. D., and Stout, A. P.: Carcinoma of the Breast, Ann. Surg. **118**: 859, 1943.
2. Daland, E. M.: Untreated Cancer of the Breast, Surg., Gynec. & Obst. **44**: 264, 1927.
3. Pack, G. T.: The Palliative Point of View About Cancer, Radiology **41**: 591, 1943.
4. Adair, F. E.: The Treatment of Metastatic and Inoperable Mammary Cancer, Am. J. Roentgenol. **27**: 517, 1932.
5. Keynes, G.: The Place of Radium in the Treatment of Cancer of the Breast, Ann. Surg. **106**: 619, 1938.
6. Martin, C. L. (Dallas, Tex.): New Developments in Irradiation Therapy of Breast Cancer, Texas State J. Med. **29**: 186, 1933.

7. Martin, C. L.: The Layer Technique in Radium Needle Therapy, Am. J. Roentgenol. **48**: 377, 1942.
8. Groover, T. A., Christie, A. C., and Merritt, E. A.: Observations on Use of Copper Filter in Roentgen Treatment of Deep Seated Malignancies, South. M. J. **15**: 440, 1922.
9. McIntosh, H. C., and Spitz, S.: Study of Radiation Pneumonitis, Am. J. Roentgenol. **41**: 605, 1939.
10. Freid, J. R., and Goldberg, H.: Post-irradiation Changes in the Lungs and Thorax, Am. J. Roentgenol. **43**: 877, 1940.
11. Warren, S., and Spencer, J.: Radiation Reaction in the Lung, Am. J. Roentgenol. **43**: 682, 1940.
12. Jacobson, V. C.: Deleterious Effects of Deep Roentgen Irradiation on Lung Structure and Function, Am. J. Roentgenol. **44**: 235, 1940.
13. Leach, J. E., Farrow, J. H., Foote, F. W., and Wawro, N. W.: Fibrosis of the Lung Following Roentgen Irradiation for Cancer of the Breast, Am. J. Roentgenol. **47**: 740, 1942.
14. Paul, L. W., and Pohle, E. A.: Radiation Osteitis of the Ribs, Radiology **38**: 543, 1942.
15. MacCarty, W. C., and Leddy, E. T.: Roentgen Treatment of Inoperable Ulcerating Carcinoma of the Breast, Radiology **39**: 711, 1942.
16. Coutard, H.: Roentgen Therapy of Epitheliomas of the Tonsillar Region, Hypopharynx and Larynx From 1920 to 1926, Am. J. Roentgenol. **27**: 313, 1832.
17. Adair, F. E.: The Effect of Preoperative Irradiation in Primary Operable Cancer of the Breast, Am. J. Roentgenol. **35**: 359, 1936.
18. Beatson, G. I.: On the Treatment of Inoperable Cases of Carcinoma of the Mamma, Lancet **2**: 104, 1896.
19. Foveau de Courmelles: Nouveau traitements physicothérapiques du cancer, Rev. méd. **20**: 91, 1910.
20. Martin, C. L., and Moursund, W. H.: Irradiation Sickness, Radiology **30**: 277, 1938.
21. Richards, G. E., and Peters, M. V.: Nembutal in the Treatment of Radiation Sickness, Am. J. Roentgenol. **35**: 522, 1936.
22. Popp, W. C.: Nausea and Vomiting Following Roentgenologic Treatment, Proc. Staff Meet., Mayo Clin. **11**: 222, 1936.
23. Dietel, F. G.: Leberextrakt gegen Röntgenketer, Strahlentherapie **48**: 110, 1933.
24. Webster, J. H. D.: X-ray Sickness Treated Successfully With Liver Extract, Brit. M. J. **1**: 15, 1934.
25. Young, B. R.: Liver Extract as a Remedy for Roentgen Sickness, Am. J. Roentgenol. **35**: 681, 1936.
26. Martin, C. L., and Moursund, W. H.: The Treatment of Roentgen Sickness With Synthetic Vitamin B_1 Hydrochloride, Am. J. Roentgenol. **38**: 620, 1937.
27. Willis, R. S., Winn, W. W., Morris, A. T., Newsom, A. A., and Massey, W. E.: Clinical Observations in Treatment of Nausea and Vomiting of Pregnancy With Vitamins B_1 and B_6, Am. J. Obst. & Gynec. **44**: 265, 1942.
28. Weinstein, B. B., Mitchell, G. J., and Sustendal, G. F.: Clinical Experiences With Pyridoxine Hydrochloride in Treatment of Nausea and Vomiting of Pregnancy, Am. J. Obst. & Gynec. **46**: 283, 1943.
29. O'Brien, F. W.: Skin Metastases in Post-operative Irradiated Breast Cancer, Radiology **30**: 437, 1938.
30. Adair, F. E.: Section on Radiation Therapy of Cancer of the Breast, Treatment of Cancer and Allied Diseases, Pack and Livingston, New York, 1940, Paul B. Hoeber, Inc.
31. Freid, J. R., and Goldberg, H.: Frequency, Clinical Cause and Treatment of Metastases From Cancer of the Breast, Am. J. Roentgenol. **50**: 499, 1943.
32. Duffy, J. J., and Lucas, C. D.: A Method of External Irradiation of the Axilla, Radiology **22**: 261, 1934.
33. Lenz, M., and Freid, J. R.: Metastases to the Skeleton, Brain and Spinal Cord From Cancer of the Breast and the Effect of Radiotherapy, Ann. Surg. **93**: 278, 1931.
34. Daland, E. M.: An Analysis of Cases at the Pondville Hospital During Its First Two Years, Am. J. Cancer **15**: 2359, 1931.
35. Dresser, R.: The Effect of Ovarian Irradiation on the Bone Metastases of Cancer of the Breast, Am. J. Roentgenol. **35**: 384, 1936.
36. Martin, C. L.: The Relation of the Endocrine System to Malignancy, Am. J. Roentgenol. **36**: 314, 1936.

THE PROBLEM OF LOCAL RECURRENCE AFTER RADICAL MASTECTOMY FOR CARCINOMA

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FOR some years I have been interested in the question of recurrence of breast cancer in the operative field, and I have been distressed by its frequency.

In the development of the present form of treatment, surgeons have, step by step attempted to remove more and more tissue in the neighborhood of the growth. Halsted introduced a radical procedure which is well known and widely followed. In this operation he removed a "large area" of the skin together with the breast, the pectoral muscles, and the axillary contents. I have been unable to find records of measurements of the skin removed for comparison with the Handley technique. Halsted's method also differed from that of Handley in that he did not advocate wide undercutting of the adjacent skin to permit plastic closure. At times I have had the privilege of observing the technique of some of his pupils and, at times, they have not removed more than a five-inch diameter of skin, which left an area that in those instances could have been closed by plastic methods if the operator had so elected. In other cases, I am certain that more than a five-inch diameter of skin was removed, to the maximum that was permissible, and yet of the fifty cases that Halsted reported in his original paper, local recurrence developed in 31.9 per cent.[1]

Handley[2] later propounded the thesis that it was not necessary to excise so much skin because cancer did not spread in the skin but in the subcutaneous tissue. He, therefore, was content to excise a circular diameter of about five inches and then dissect in a peripheral direction in the subcutaneous tissue so as to leave a flap of skin that could be approximated in most instances. In my practice, I fell under his influence and have followed this method in regard to the skin. However, in small breasts with the removal of such a diameter of skin, I have found it necessary to graft skin.

As time passed, I became more and more interested in the question of the correctness of Handley's position and also that of Halsted. In truth, I have never seen definite proof, in pathologic sections, that cancer spreads in the skin lymphatics or in the subcutaneous lymphatics. But from clinical observations, I am inclined to favor Handley's contention. My bias in favor of skin closure when feasible may have influenced this judgment. If so, I might be proved definitely wrong by the results in our clinic and elsewhere.

Generally speaking, our five-year survival results were comparable to those of the other clinics, when the mathematical statistical errors are considered that creep into a report of less than 10,000 cases. We were satisfied that our results were comparable, but then I began to wonder about the significance

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of local recurrences. Theoretically, if an operation is correct it should excise all the local cancer in an operable field. But we found that there was a definite incidence of local recurrence in our patients, in whom we had used the Handley technique.

In a study of 238 cases of plastic closure (Handley) that had been followed for a minimum time of five years, and many much longer, we had evidence of 22.6 per cent local recurrence.

It may be contended that 22.6 per cent local recurrence in the 238 cases indicated that our type of radical operation was inadequate. Therefore, as a check on our results, I have compared these results with those from other clinics (Table I).

TABLE I. RESULTS OF RADICAL OPERATION FOR BREAST CANCER

HOSPITAL		LOCAL RECURRENCE		FIVE YEAR FREEDOM	
		NUMBER	PER CENT	NUMBER	PER CENT
The Roosevelt Hospital[3] (New York)					
(Plastic closure)					
Limited to breast	101	11	10.8	62	61
Axilla involved	137	43	31.5	24	17
The Presbyterian Hospital[4] (New York)					
(Plastic closure and skin graft)					
Limited to breast	237	23	9.7	145	61.2
Axilla involved	385	120	31.3	81	21
The St. Lukes Hospital[5] (New York)					
(Plastic closure and skin graft)					
Limited to breast	116	8	6.9	68	58.6
Axilla involved	244	52	21.3	57	23.3
The Henry Ford Hospital[6] (Detroit)					
(Plastic closure and skin graft)					
Limited to breast	97	6	6.1		
Axilla involved	149	31	20.8		
(Plastic closure)		4	5.5		
Limited to breast	72				
Axilla involved	67	18	27		
(Skin graft)					
Limited to breast	24	2	8.3		
Axilla involved	67	18	27		
Johns Hopkins Hospital[1]					
(Table XXX)					
Plastic closure	116	46	39.7		
Thiersch graft	322	97	30.1		
(There is no breakdown into two groups; limited to breast and axilla involved)					
J. Stewart Rodman[7]					
(Rodman operation)					
W. L. Rodman plastic closure	132	3	2.2		

The question of local recurrence (or persistence of carcinoma, as Hugh Auchincloss[9] has so aptly phrased it) is of interest from several angles. The surgeon is likely to consider a recurrence as a reflection on his lack of thoroughness and radicalism. It often may be so. But it must also be recognized that the most radical of surgeons cannot clean out the intercostal and intermammary nodes without removing the chest wall!

Then too, it is interesting to note the increase in the percentage of general and local recurrence the longer the cases have been followed. Like others, some of my patients have had local recurrences in the scar and adjacent skin at eleven, thirteen, and seventeen years after operation. But in only one

instance have I seen local recurrence alone. That patient had a local recurrence at eleven years, with excision, and freedom from disease, now seven years. The numerous other patients shortly revealed evidence of cancer elsewhere.

It is possible that cancer may lie dormant in subcutaneous or dermal tissue for many years and then flare up into renewed activity. Some day the biochemist may be able to give an answer to this clinical observation.

It is not my thought to weigh too carefully the variations in percentage except in a broad way. It may be pointed out that regardless of the Halsted or the Handley approach, there is a high incidence of local recurrence, and that there is no proof that one method is better than the other in avoiding local recurrence. It is also, I think, fair to believe that in cases with axillary metastases the local recurrence rate is tripled over those in which the cancer is limited to the breast.

It is a proper method to break down the cancer into two obvious groups: (1) limited to the breast, and (2) breast plus axillary metastases. At best this is a crude method for it must be recognized that cancer spreads by embolism to the lymph nodes along the intercostal and internal mammary spaces as well. It must always be borne in mind that the pathologic process is often more widespread than can be detected by either the clinician or the pathologist. It must also be admitted that there are limitations to the amount of surgery.

In our report of cases we have some support of our contention in the matter of local recurrence in patients with axillary metastases. It would seem to point to widespread emboli in the chest area. We have all along recognized that this index was crude, and acknowledged that at times we were innocently operating on patients who had already reached the stage of inoperability.

Recently, I have had an experience that threw some light on this subject.

CASE REPORT

Mrs. A. had a tumor in the right breast with axillary metastases.[8] At operation a biopsy was performed with a needle charged with a high-frequency current. The skin wound was then closed. Drapes were removed and the breast area was prepared again. Gowns, gloves, and instruments were changed, as if in preparation for another operation. The radical operation was then performed after the frozen section diagnosis of cancer had been made by the pathologist (Brandes). At the end of the operation, it became obvious that a skin graft would be necessary. The left thigh was prepared by an assistant, after which the operator, *without changing gloves,* took the Padgett-Hood dermatome and removed a suitable area of skin in one piece. Sulfathiazole ointment was applied to this raw skin by an assistant and the physician completed the operation. Three months later this patient developed adenocarcinoma on the donor site. In the operation no carcinoma tissue was seen as the incision had gone wide of the biopsy site. It is true that there were involved lymph nodes in the axilla which had been removed en bloc from the apex of the axilla downward and outward. It is fair to assume that some invisible cancer tracks had been cut through and that some of these cells adhered to the gloves, and were transplanted to the raw area on the thigh at the time that the graft was taken.

To draw an analogy from this case, it is fair to assume that in the course of a radical operation one must not infrequently cut through invisible cancer

tracks, and that some cancer cells deposit on the knife or gloves, to be deposited later about the raw wound. In an attempt to avoid this, we have made a practice of using arterial clamps only once, but we have not changed gloves frequently. We have used four or five scalpels in the course of an operation. It might be indicated to use many more. I believe now that one source of local recurrence is the unconscious deposit of cells about the wound.

It might be contended, with considerable truth, that in these cases we are operating in inoperable cases, even though we have no physical method of detection at the time of operation. Methods of technique for avoidance of cancer cells are as strongly indicated as avoidance of pus cells, but methods only are available. We can see neither. Theoretically, the endotherm needle might help to avoid this hazard, through cauterization and destruction of tissue. To date there has not been sufficient evidence to support this theory.

To return to the relationship of local recurrence to an initial widespread of the cancer at the time of the initial operation, I have observed that the local recurrence has been in association with the presence of metastases outside the operative field in every case in this series, except one. This exception was in a woman who had no axillary metastases at the initial operation. She was free from the disease for eleven years when she developed a local recurrence in the scar. This was excised and now, seven years later, she is well and free from signs of cancer.

We have also observed, with others, the development of cancer metastases in distant points such as the upper end of the femur, only to have local recurrence appear a year or two later. The longer a series of cases if followed, the higher will be the percentage of local recurrence.

Before the advent of roentgen therapy there was local recurrence. As the technique developed it was hoped by all of us that the thorough treatment of the operative field would reduce if not eliminate local recurrence. At least in that area roentgen therapy should prove itself. It has been our experience that such has not been the case. We have the same high incidence of local recurrence after the use of postoperative x-ray therapy.

SUMMARY

Local recurrence of breast cancer after radical mastectomy is a common experience in all clinics.

A chest without a skin graft is preferable to one with a skin graft. With the Handley technique it is usually possible to make a plastic skin closure.

As far as can be found out, there is no sufficient proof yet that the Halsted skin removal with Thiersch graft gives a reduced incidence of local recurrence over the plastic skin closure of Handley.

It is my belief that local recurrence after a proper radical operation such as the Halsted or Handley procedure is due to first, the physical impossibility of removing all cancerous tissue in the internal mammary and intercostal areas. In other words, we are dealing in such cases with undetectable, inoperable extension of the cancer; second, the transplantation of cancer cells that have

been cut into in the course of the operation. This frequency should be reduced by improved "cancer asepsis."

REFERENCES

1. Lewis, Dean, and Rienhoff, William Francis, Jr.: A Study of the Results of Operations for the Cure of Cancer of the Breast, Ann. Surg. **95**: 336, 1932.
2. Handley, W. Sampson: Cancer of the Breast and Its Treatment, New York, 1922, Paul B. Hoeber.
3. White, W. C.: Skin Removal in Radical Mastectomy, Ann. Surg. **115**: 1182, 1942.
4. Haagensen, C. D., and Stout, A. P.: Carcinoma of the Breast, Ann. Surg. **116**: 801, 1942.
5. Shore, B. R.: Carcinoma of the Breast, Surg., Gynec., Obst. **71**: 515, 1940.
6. Hoopes, B. F., and McGraw, A. B.: The Halsted Radical Mastectomy, SURGERY **12**: 892, 1942.
7. Rodman, J. S.: Skin Removal in Radical Breast Amputation, Ann. Surg. **118**: 694, 1943.
8. Brandes, Walter W., White, W. C., and Sutton, J. B.: Accidental Transplantation of Carcinoma in the Operating Room, Surg., Gynec. & Obst. **82**: 1946.
9. Auchincloss, Hugh, in White, W. C.: Postoperative Irradiation in Breast Cancer, Discussion, Ann. Surg. **108**: 31, 1938.

SURVIVAL RATES OF RADICAL MASTECTOMY FOR UNILATERAL AND BILATERAL CARCINOMA OF THE BREAST

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THE mammary gland is one of the most common sites of malignant disease in women. There are essentially two types of primary malignant neoplasm of the breast: carcinoma and sarcoma. Carcinoma is the principal type of malignant lesion occurring in the mammary gland. The different types of malignant lesions of the breast found in 6,558 patients on whom operation was performed at the Mayo Clinic from 1910 to 1940, inclusive, are shown in Table I.

TABLE I. MALIGNANT LESIONS OF THE BREAST (1910-1940 INCLUSIVE); RADICAL MASTECTOMY, TOTAL SERIES PATHOLOGIC DIAGNOSIS

TYPE OF LESION	NUMBER	PER CENT
Adenocarcinoma	6,412*	97.78
Epithelioma	31	0.47
Paget's disease	69	1.05
Melanoepithelioma	3	0.05
Sarcoma	39	0.59
Carcinosarcoma	4	0.06
Total	6,558	100.00

*Includes 21 cases in which the pathologic diagnosis was made elsewhere.

The relative frequency of occurrence of the different types of carcinoma constituting 99.4 per cent of the total 6,558 malignant lesions of the breast in this series is very important from the standpoint of prognosis because this type of malignant neoplasm is prone to metastasize early to distant parts of the body, a fact that emphasizes the importance of early recognition and immediate treatment of malignant disease of the breast.

The results of treatment of malignant disease of the breast have been markedly improved by radical surgical treatment. Since the introduction of this method by Halsted, it has been the method most generally accepted by the medical profession.

This radical surgical treatment is based on the hypothesis that the malignant lesion is localized at the onset but that later in the course of the disease it invades other tissues by transmission through the lymph stream and occasionally through the blood stream. If this conception of the disease is correct, it is manifest that the most important considerations in the treatment are early recognition and immediate complete removal of the diseased tissues. One of the principal reasons for failure of surgical operation to accomplish this objective uniformly is the high percentage of cases in which metastasis has occurred before the patient is operated upon. If the condition is confined to the breast at the time of operation, complete eradication of the disease can be expected.

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From a surgical standpoint lesions of the breast may be divided into two general groups. The first group consists of those that can be definitely diagnosed clinically as malignant lesions. These are best treated by immediate primary radical mastectomy.

The second group consists of those lesions in which a definite diagnosis cannot be established on the basis of the clinical manifestations of the disease. This is the most important group from a surgical standpoint as the lesions are usually early and the most satisfactory operative results can be obtained from surgical treatment of these lesions. As I have stated before, in all cases in which there is a single localized tumor, the lesion should be completely removed by wide surgical excision and a definite diagnosis immediately established by microscopic examination from frozen sections of the tissue. If the lesion is found to be malignant, the operation should be completed immediately as a radical amputation.

From the standpoint of operative procedure the best surgical results are obtained from primary radical amputation. There are many variations in methods of carrying out the minor details of the radical amputation but the fundamental principles of the operation are invariable and should be carried out in all cases accepted for surgical treatment. This as an initial treatment is by far the most important procedure and the possibility of a cure depends on the thoroughness with which it is carried out. The importance of this cannot be overestimated, for secondary operative procedures are rarely curative. I believe that one of the important factors in the unsatisfactory results obtained from surgical treatment is the relative frequency with which minor operations are done for malignant disease.

The number of inoperable cancers of the breast that have been seen at the clinic during the last five years has remained fairly constant. There are varied opinions as to what constitutes operability. I shall state briefly the criteria of operability that have been followed in this series of cases. Any lesion of the breast was considered to be operable if it was freely movable from the thoracic wall regardless of ulceration. In some cases even if there were cutaneous nodules proximal to the tumor, regardless of the presence or absence of palpable axillary lymph nodes, the lesion was considered operable. In addition, patients were accepted for operation if they had a diffuse type of malignant growth, if malignant disease was associated with lactation, as well as if malignant disease was associated with pregnancy. Those conditions were considered to be inoperable in which a large growth was fixed to the thoracic wall and there was very extensive metastasis to the axillary and supraclavicular lymph nodes or metastasis to other distant parts of the body. A few patients who had metastasis that involved distant portions of the body were accepted for operation because of exceptional circumstances.

As thus indicated, it is difficult to draw any sharp line between operable and inoperable lesions and in each case treatment must be according to the findings. I have accepted for operation all patients to whom, I felt, there was a reasonable chance of offering comfort or greater length of life as well as

those whose disease, I felt, stood a reasonable chance of being cured. It may seem that these rules of operability have not been drawn strictly enough and that cases have been accepted for operation in which the growth is too extensive. This is a matter of opinion, however, and justification has been found in many cases in which the condition was thought to be absolutely hopeless before operation but in which the patients have lived to enjoy many years of comfort.

There are many factors that influence the results of surgical treatment, the more important of which are as follows: (1) the extent of the malignant involvement at the time of operation, (2) the thoroughness with which the radical operation is done, (3) the degree of malignancy as shown by microscopic examination of the primary lesion, (4) the presence of other associated conditions such as pregnancy, (5) the general constitutional diseases such as diabetes, (6) the age of the patient.

Statistical studies of the results of treatment of mass groups of patients are often misleading. This is particularly true when comparing the results obtained from different types of treatment; in these studies it is imperative that only similar groups of cases be used for comparison. I do not believe that comparative studies are of value unless it is definitely known that the groups compared are similar as to type and extent of the disease.

There are unavoidable inaccuracies in statistical studies because of the difficulty in obtaining accurate classifications of cases due to the many factors that influence prognosis as well as the difficulty in obtaining 100 per cent follow-up records of cases in which operation was performed, but these studies are the most valuable method we have of determining the results obtained from treatment. Their value is in direct proportion to the accuracy of classification, the completeness of the follow-up, and the length of time that has elapsed since treatment was instituted.

For the past nineteen years I have made statistical studies at about two-year intervals of the cases of carcinoma of the breast in which operation was performed at the Mayo Clinic. However, because of the influence of war conditions, an interval of four years has elapsed since the last study. There has been a slight decrease in the percentage of follow-ups from 98.5 to 97.1 per cent of traced patients. Even the latter percentage, however, I believe is a very high proportion because of the size of the series and present-day difficulties of contacting patients because of changes of residence.

The following statistical studies have been made on all patients on whom operation has been performed at the clinic for malignant disease of the breast from the years 1910 to 1940, inclusive, and comprise a series of 6,558 cases. Forty-seven patients (0.7 per cent) died in the hospital following operation; of the 6,511 patients who recovered from operation 6,318 (97.0 per cent) have been traced three or more years.

These studies have been made primarily to determine the results of radical surgical treatment as well as to point out some of the clinical or pathologic factors that influence the prognosis. In all of the statistical studies of survival

rates it has been assumed that the patient died of malignant disease although in many instances it was definitely known that death was due to other causes.

I should like to express my appreciation to the division of biometry and medical statistics for their diligence in searching for these records and in obtaining such a remarkably high percentage of traced patients.

The study of survival rates for the various periods after operation was made in the following manner. The records of patients on whom operation had been performed the requisite number of years prior to the time of inquiry, which was Jan. 1, 1944, were first selected. For the calculation of the three-year survival rate, the patients treated in 1940 or earlier were selected; for the five-year survival rate, those operated upon in 1938 or earlier were selected; for the ten-year survival rate, those operated on in 1933 or earlier were selected, and so forth. Obviously, then, the three-year survival rate was calculated on a larger number of patients than the five-year survival rate; the five-year rate was calculated on a larger number of patients than the ten-year survival rate and so forth. Of the patients operated upon, anyone not traced for a sufficient number of years after operation was considered untraced and was not included in the calculation of the survival rate. For instance, in calculating the five-year survival rate, a patient who had been operated on seven years prior to the time of inquiry but had been traced for only four years after operation, and who was living at that time, was considered untraced in the calculation of the five-year survival rate, because it is not known whether that patient did or did not survive until the fifth year after operation. For the purposes of the calculation of the three-year survival rate, that patient was considered traced, for it is known that the patient survived more than three years after operation.

When patients did not answer the routine follow-up letter, the local department of health, bureaus of vital statistics, and so forth were consulted to learn whether any record of death existed. In the end, only a small fraction of the patients remained untraced. Ninety-seven per cent of the patients on whom operation had been performed three or more years before investigation were traced for the requisite period.

The first study was made on the entire series of malignant lesions of the breast treated by radical mastectomy from 1910 to 1940, inclusive. All cases are included in this table, carcinoma, sarcoma, unilateral and bilateral disease, females and males. The special group studies which are shown later are included in this table. The objective of this study was to determine the influence that the extent of the disease, as indicated by the presence of axillary nodal metastasis, when found at the time of the operation, had on prognosis. The results of this study are shown in Table II, which gives for the three-year, five-year, ten-year, fifteen-year and twenty-year survivals, the number of patients on whom operation was performed, those traced, and the number who survived, with the respective percentages. This is the only table of survival rates in which the complete tabulation of these different numbers of patients will be included. In the subsequent tables that deal with survivals, only the

TABLE II. MALIGNANT LESIONS OF THE BREAST, RADICAL MASTECTOMY—MALES AND FEMALES, CARCINOMA

AXILLARY METASTASIS	PATIENTS OPERATED ON*	PATIENTS TRACED	LIVED 3 OR MORE YEARS AFTER OPERATION: PATIENTS	LIVED 3 OR MORE YEARS AFTER OPERATION: PER CENT OF TRACED PATIENTS	PATIENTS OPERATED ON	PATIENTS TRACED	LIVED 5 OR MORE YEARS AFTER OPERATION: PATIENTS	LIVED 5 OR MORE YEARS AFTER OPERATION: PER CENT OF TRACED PATIENTS
Present (60%)	3,897	3,790	1,717	45.3	3,593	3,511	1,072	30.5
Absent (40%)	2,614	2,528	2,148	85.0	2,302	2,223	1,685	75.8
Total	6,511	6,318	3,865	61.2	5,895	5,734	2,757	48.1

*Inquiry as of Jan. 1, 1944. The three-year group comprises the patients on whom operation was performed three or more years prior to the time of inquiry, that is, 1940 or earlier; the five-year group comprises those on whom operation was performed in 1938 or earlier; the ten-year group comprises those on whom operation was performed in 1933 or earlier and so forth. Ninety-seven per cent of all patients were traced. The 47 patients who died in the hospital following operation (1910-1940) are excluded in the calculation of survival rates.

number of patients traced and the percentage of survivals will be given, in order to simplify the tables.

As is seen in Table II, there were, for the calculation of the three-year survival rate, 6,511 patients with malignant lesions of the breast on whom operation was performed in 1940 or earlier, of whom 6,318 (or 97.0 per cent) were traced. There was a wide variation in the survival results and the prognosis was much better in those cases in which axillary nodal metastasis was not found at the time of operation than it was in those cases in which axillary nodal metastasis was found. The patients who did not have axillary metastasis at the time of operation constituted 40 per cent of the entire series. The proportion of this group of patients living three years or more after operation was 85.0 per cent, or almost twice as large as that for the group with axillary metastasis, which was 45.3 per cent. In the five-, ten-, fifteen-, and twenty-year survival rates of patients without axillary nodal metastasis, it was found that the improvement increased progressively over the group with axillary metastasis. For the five-year period, the survival rate for the group without metastasis was two and one-half times as large as that for the group with metastasis; for the ten-year period it was three and one-half times as large; for the fifteen-year period it was four times as large, and for the twenty-year period it was more than five times as large.

Although axillary nodal metastasis is only one of the factors that may indicate the extent of the disease at the time of operation, I believe that it is one of the most important factors indicating the prognosis following operation because of the great influence that it has on the survival rates. Because of this fact, in compiling statistical studies of survival rates of malignant disease of the breast, I believe that all cases should be divided into two main groups, those with and those without axillary nodal metastasis at the time of operation, and that statistical studies should never be based on a combination of the groups, without knowing the number of patients in each group.

Accordingly, in all of the following studies of different classifications and types of carcinoma, the cases in each classification have been divided into two

AND SARCOMA, UNILATERAL AND BILATERAL DISEASE, SURVIVAL RATES ACCORDING TO AXILLARY METASTASIS

		LIVED 10 OR MORE YEARS AFTER OPERATION				LIVED 15 OR MORE YEARS AFTER OPERATION				LIVED 20 OR MORE YEARS AFTER OPERATION	
PATIENTS OPERATED ON	PATIENTS TRACED	PATIENTS	PER CENT OF TRACED PATIENTS	PATIENTS OPERATED ON	PATIENTS TRACED	PATIENTS	PER CENT OF TRACED PATIENTS	PATIENTS OPERATED ON	PATIENTS TRACED	PATIENTS	PER CENT OF TRACED PATIENTS
2,940	2,894	478	16.5	2,284	2,243	250	11.1	1,502	1,468	96	6.5
1,717	1,647	959	58.2	1,258	1,200	532	44.3	858	816	272	33.3
4,657	4,541	1,437	31.6	3,542	3,443	782	22.7	2,360	2,284	368	16.1

groups, those with and those without axillary nodal metastasis at the time of operation.

UNILATERAL CARCINOMA OF THE BREAST IN WOMEN

A study was made of all women patients who had unilateral carcinoma of the breast, to determine the results of radical mastectomy for this group of patients. The results of this study are shown in Table III. This study comprises a series of 6,149 patients or 93.8 per cent of the entire series of malignant lesions of the breast. Of these 6,149 patients, 5,970 (or 97.1 per cent) have been traced three or more years. Of the patients, 3,722 (or 60.5 per cent) were found to have axillary nodal metastasis at the time of operation and 2,427 patients (39.5 per cent) were not found to have axillary nodal metastasis at the time of operation. The three-year, five-year, ten-year, fifteen-year, and twenty-year results were very similar, varying only a fraction of a per cent from those in the entire series as shown in Table II. In those cases in which axillary metastasis was not present at the time of operation the results were much better than in those cases in which axillary nodal metastasis was present.

A study was made to determine if there was any difference in the results obtained in the different grades of carcinoma of the breast. I shall first give a brief summary of the grading of cases, which has been done according to Broders' method of dividing malignant lesions into four grades based on cellular differentiation. This part of the study is based on 5,134 cases, the total number that has been graded in the series of unilateral carcinoma in women. A study was also made to determine the percentage of cases in each of the four grades of malignancy and the percentage of each grade of malignancy with and without axillary nodal metastasis at the time of operation. The results of this study are shown in Table IV. It was found that 49.2 per cent, or nearly one-half of all carcinoma of the breast in this series, is of grade 4 malignancy and that of these grade 4 lesions axillary nodal metastasis was found in 84.1 per cent of cases at the time of the operation. On adding the grade 3 and 4 lesions, it was found that 81.7 per cent of carcinoma of the breast was of high grade malignancy from which metastasis occurred early. This again emphasizes the seriousness of malignant disease of the breast in

that the majority of the lesions are of a high grade of malignancy and present a high percentage of axillary nodal metastasis at the time of operation.

A study was then made to determine the survival rates according to the four grades of malignancy. The two main groups (those with and those without axillary nodal metastasis) were each subdivided into four groups, making eight classes in all. I believe that the comparison of results of any type of

TABLE III. UNILATERAL CARCINOMA OF THE BREAST IN WOMEN; SURVIVAL RATE FOR DIFFERENT PERIODS AFTER RADICAL MASTECTOMY; A COMPARISON OF RATES IN GROUPS WITH AND WITHOUT AXILLARY METASTASIS*

AXILLARY METASTASIS	TOTAL	3 YEARS		5 YEARS		10 YEARS		15 YEARS		20 YEARS	
		PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS
Present (60.5%)	3,722	3,619	45.1	3,348	30.4	2,757	16.4	2,132	11.1	1,392	6.5
Absent (39.5%)	2,427	2,351	85.1	2,059	75.7	1,521	57.9	1,119	44.4	759	33.5
Total	6,149	5,970	60.9	5,407	47.6	4,278	31.1	3,251	22.5	2,151	16.0

*Only patients operated on and traced for the different periods are included in this table.

TABLE IV. UNILATERAL CARCINOMA OF THE BREAST (1910-1940 INCLUSIVE); RADICAL MASTECTOMY, METASTASIS IN WOMEN BY GRADE OF MALIGNANCY

	TOTAL SERIES		WITH METASTASIS		WITHOUT METASTASIS	
	NUMBER	PER CENT OF TOTAL GRADED CASES	NUMBER	PER CENT OF RESPECTIVE GRADE	NUMBER	PER CENT OF RESPECTIVE GRADE
Grade 1	287	5.6	13	4.5	274	95.5
Grade 2	653	12.7	233	35.7	420	64.3
Grade 3	1,666	32.5	1,078	64.7	588	35.3
Grade 4	2,528	49.2	2,127	84.1	401	15.9
Total graded cases*	5,134	100.0	3,451	67.2	1,683	32.8

*In 1,061 cases, grade of malignancy was not stated.

TABLE V. RADICAL MASTECTOMY FOR UNILATERAL CARCINOMA OF THE BREAST OF WOMEN; A COMPARISON OF SURVIVAL RATES ACCORDING TO GRADE OF MALIGNANCY WITH AND WITHOUT AXILLARY METASTASIS*

AXILLARY METASTASIS	3 YEARS		5 YEARS		10 YEARS		15 YEARS		20 YEARS	
	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS
Present:										
Grade 1	13	92.3	12	100.0	11	63.6	10	40.0	8	25.0
Grade 2	228	70.6	209	53.1	185	34.6	160	24.4	131	14.5
Grade 3	1,039	55.1	933	35.3	777	17.6	620	10.6	423	5.2
Grade 4	2,048	37.1	1,903	24.9	1,495	12.5	1,063	8.2	687	5.1
Absent:										
Grade 1	261	96.9	203	95.1	108	88.0	58	74.1	36	55.6
Grade 2	407	91.6	348	84.2	231	65.8	120	44.2	47	25.5
Grade 3	563	82.8	468	70.5	287	50.9	159	37.1	81	28.4
Grade 4	383	75.7	309	62.8	193	43.0	132	30.3	81	21.0

*Only patients operated on and traced for the different periods are included in this table. Total patients operated on: 6,149, of whom 5,970 were traced. Of those traced, in 1,028 the grade of malignancy was not stated.

treatment is most accurate when made according to this classification. Table V shows the results over periods of three, five, ten, fifteen, and twenty years according to the grade of malignancy and the presence or absence of axillary nodal metastasis at the time of operation. This shows a definite and uniform relationship between the operative results and the degree of malignancy, in that the lower the degree of malignancy the higher the percentage of patients alive three, five, ten, fifteen, and twenty years after operation. This was found to be true in both the groups with and without axillary metastasis.

It also shows, as was revealed in the previous studies, that the surgical results are much more satisfactory in cases without lymphatic involvement than in those with lymphatic involvement in the same grade of malignancy. The study shows that the grading of malignant lesions gives a very important indication as to the prognosis. I believe that the grading of malignant lesions represents one of the greatest advances that has been made in the study of malignant disease in recent years.

A study was made of all women patients who had had radical mastectomy for unilateral carcinoma of the breast between the years 1910 and 1940, inclusive, to determine the influence of age of the patient on the incidence of occurrence and results of operation. This constitutes a series of 6,195 patients, as is shown in Table VI. The youngest patient was 16 years and the oldest

TABLE VI. UNILATERAL CARCINOMA OF THE BREAST IN WOMEN; RADICAL MASTECTOMY (1910-1940 INCLUSIVE), AGE DISTRIBUTION AND INCIDENCE OF METASTASIS ACCORDING TO AGE

AGE (YEARS)	TOTAL PATIENTS	PER CENT	WITH METASTASIS	
			NUMBER	PER CENT
16-19	5	0.1	1	20.0
20-29	103	1.7	47	45.6
30-39	837	13.5	507	60.6
40-49	2,029	32.7	1,220	60.1
50-59	1,803	29.1	1,158	64.2
60-69	1,116	18.0	672	60.2
70-79	292	4.7	146	50.0
80-87	10	0.2	4	40.0
Total	6,195	100.0	3,755	60.6
Mean age 51.3 years				

was 87 years of age. In 32.7 per cent of the entire series the disease occurred in the fifth decade of life. This is the decade of life that presented the highest incidence of occurrence. The mean age of the entire series was 51.3 years. The highest incidence of metastasis found at the time of the operation in the different decades of life was 64.2 per cent and was found in patients from 50 to 59 years of age, inclusive. In 60.6 per cent of the entire series axillary nodal metastasis was found at the time of operation.

A study was made to determine the five-year survival rates according to age. This study was made on a series of 5,558 women patients, of whom 5,407 were traced. These patients had had radical mastectomy for unilateral carcinoma of the breast from 1910 to 1938, inclusive, which permits the compiling of five-year survival rates. The results of this study are shown in Table VII. This study shows that in patients having axillary nodal metastasis at the time

TABLE VII. UNILATERAL CARCINOMA OF THE BREAST IN WOMEN; FIVE-YEAR SURVIVAL RATES ACCORDING TO AGE

AGE (YEARS)	WITH METASTASIS			WITHOUT METASTASIS			TOTAL SERIES		
	PATIENTS TRACED	LIVED 5 YEARS OR MORE AFTER OPERATION		PATIENTS TRACED	LIVED 5 YEARS OR MORE AFTER OPERATION		PATIENTS TRACED	LIVED 5 YEARS OR MORE AFTER OPERATION	
		NUMBER	PER CENT		NUMBER	PER CENT		NUMBER	PER CENT
16-19	1	0	–	4	4	100.0	5	4	80.0
20-29	45	13	28.9	43	40	93.0	88	53	60.2
30-39	466	106	22.7	281	219	77.9	747	325	43.5
40-49	1,102	334	30.3	699	571	81.7	1,801	905	50.2
50-59	1,029	341	33.1	549	403	73.4	1,578	744	47.1
60-69	577	189	32.8	356	252	70.8	933	441	47.3
70-79	125	34	27.2	122	69	56.6	247	103	41.7
80-87	3	0	–	5	1	20.0	8	1	12.5
Total	3,348	1,017	30.4	2,059	1,559	75.7	5,407	2,576	47.6

of operation, the highest percentage of five-year survivals was in the sixth decade of life. In patients presenting no axillary nodal metastasis, the highest percentage of five-year survivals was in the second and third decades of life. However, in these decades of life there is a relatively small percentage of patients compared with the later decades of life. The best results in the later decades of life were obtained in the fifth decade, in which the proportion of five-year survivals was 81.7 per cent. This is also the decade of life that carries the greatest incidence of the disease.

A quinquennial study from the years 1910 to 1939 was made of some of the clinical and pathologic considerations to determine what change, if any, had taken place in these periods. This study is recorded in Table VIII and

TABLE VIII. UNILATERAL CARCINOMA OF THE BREAST IN WOMEN; RADICAL MASTECTOMY (1910-1940)

YEAR	TOTAL CASES	PER CENT WITH METASTASIS	PER CENT WITH GRADES 3 AND 4	MEAN AGE (YEARS)	PER CENT UNDER 50 YEARS	DURATION OF SYMPTOMS	
						PER CENT UNDER 6 MONTHS	PER CENT UNDER 1 YEAR
1910-1914	527	58.3	87.8	51.0	50.7	32.6	54.3
1915-1919	900	66.7	84.1	50.2	52.8	41.6	63.0
1920-1924	1,026	64.6	84.8	50.6	50.6	44.5	62.7
1925-1929	1,164	65.5	82.4	51.1	48.3	49.7	65.4
1930-1934	1,028	60.3	80.4	51.9	43.8	49.6	68.1
1935-1939	1,265	52.4	79.0	51.9	46.2	56.4	70.4
Total	5,910	61.2	82.0	51.2	48.3	47.5	65.1

shows very little change in the mean age of patients but it does show some tendency to an increase in age of patients at the time of operation in the past ten years. This is also reflected in the decreasing percentage of patients less than 50 years of age at the time of operation. It is gratifying to see that there was an appreciable decrease in the percentage of patients having axillary nodal metastasis in the past five-year period studied (1935-1939), it being 52.4 per cent as compared with 61.2 per cent of the total for the entire period, a fact that indicates that the educational program in which the medical pro-

fession has participated is showing favorable results in that physicians are seeing patients earlier in the course of the disease. This is also reflected in that there was a higher percentage of patients, 56.4 per cent, operated on within six months after the onset of symptoms during the last five-year period and 70.4 per cent within one year as compared with 47.5 and 65.1 per cent of the total periods in these respective groups. It is also found that there has been a tendency toward a lower percentage of grades 3 and 4 malignancies in the past fifteen years.

A quinquennial study was made of unilateral carcinoma of the breast in women who had had radical mastectomy from 1910 to 1938, inclusive. The last period is only four years (1935-1938) because patients operated on in 1939 had not been operated on for a sufficient length of time to enable five-year results to be compiled. This study was made up of 5,558 patients of whom 5,407 were traced. The patients are divided into the two groups, those with and those without axillary nodal metastasis at the time of operation, as is shown in Table IX. It was found that there was a consistent and appreciable

TABLE IX. UNILATERAL CARCINOMA OF BREAST, RADICAL MASTECTOMY; FIVE-YEAR SURVIVAL RATES FOR DIFFERENT PERIODS OF EXPERIENCE ACCORDING TO METASTASIS

PERIOD IN WHICH OPERATION WAS PERFORMED	WITH METASTASIS			WITHOUT METASTASIS			TOTAL SERIES		
	PATIENTS TRACED	LIVED 5 YEARS OR MORE AFTER OPERATION		PATIENTS TRACED	LIVED 5 YEARS OR MORE AFTER OPERATION		PATIENTS TRACED	LIVED 5 YEARS OR MORE AFTER OPERATION	
		NUMBER	PER CENT		NUMBER	PER CENT		NUMBER	PER CENT
1910-1914	300	71	23.7	212	133	62.7	512	204	39.8
1915-1919	586	155	26.5	292	211	72.3	878	366	41.7
1920-1924	650	155	23.8	356	252	70.8	1,006	407	40.5
1925-1929	750	245	32.7	395	305	77.2	1,145	550	48.0
1930-1934	607	213	35.1	396	324	81.8	1,003	537	53.5
1935-1938 (4 years)	455	178	39.1	408	334	81.9	863	512	59.3
Total	3,348	1,017	30.4	2,059	1,559	75.7	5,407	2,576	47.6

improvement in the results obtained from radical mastectomy in each of the five-year periods. The study of patients presenting axillary nodal metastasis at the time of operation from 1910 to 1914, inclusive, shows that 23.7 per cent were living five years after operation as compared with 39.1 per cent of those on whom operation was performed during 1935 to 1938, inclusive. In this study the results obtained in patients without nodal metastasis at the time of operation show a greater improvement in that there was 62.7 per cent of five-year survivals from 1910 to 1914 as compared with 81.9 per cent from 1935 to 1938.

BILATERAL CARCINOMA

The results of the surgical treatment of bilateral carcinoma of the breast are shown for two classifications: (1) those in which the carcinoma occurred in the second breast at a later time, or nonsimultaneous carcinoma, and (2) those in which the carcinoma occurred in both breasts at the same time, designated as "simultaneous" carcinoma of the breast.

Nonsimultaneous.—The occurrence of nonsimultaneous carcinoma of the breast presents a very important problem in that some surgeons advocate the routine removal of the remaining breast in all patients on whom radical removal of one breast has been performed. I have made a special study of this group of patients in order to determine the incidence as well as the results of radical mastectomy for primary carcinoma of the remaining breast. The study of this group of cases has been divided into two main groups, in order to obtain as accurate an evaluation of results as possible. The first group consisted of patients who had both operations of radical mastectomy done at the Mayo Clinic. This consisted of a series of 155 patients. The intervals between the operations were from one to twenty-eight years.

The second group consisted of those patients who had either the first or the second operation done elsewhere. This comprised a series of fifty-seven patients. We have made a special effort in this latter group to determine definitely that the operation done elsewhere was for carcinoma and only those cases in which we had definite knowledge that the operation which was done elsewhere was for carcinoma have been compiled. In a previous paper, which I published in the *Pennsylvania Medical Journal*, January, 1940, this group of cases was larger. In the present study a number of these patients have been reclassified and have been retained in the group of unilateral carcinoma because of the lack of definite evidence that the operation done elsewhere was for carcinoma.

The entire group of nonsimultaneous carcinoma in this series is 212 cases and, when compared with unilateral carcinoma of 6,149 patients of this series, is 3.4 per cent. This, however, is the incidence of operable carcinoma occurring in the remaining breast in this series and not the actual incidence of carcinoma occurring in the remaining breast as there is probably an equal number of cases, if not a greater number, in which carcinoma of the remaining breast developed but which are inoperable because of distant metastasis from the first side. It has been impossible to determine accurately the percentage of this latter group of carcinoma occurring in the remaining breast but it is probable that the actual incidence is from 6 to 8 per cent. This percentage, while relatively high, does not warrant routine mastectomy of the remaining breast but it does indicate the importance of a routine follow-up examination on all patients on whom radical mastectomy has been performed for unilateral carcinoma of the breast.

The results of the study of the survival rates of women patients who had bilateral radical mastectomy for nonsimultaneous carcinoma of the breast in which both operations were done at the clinic are shown in Table X. There were 155 patients, all of whom were traced. The three-, five-, ten-, fifteen-, and twenty-year survival rates of this group were very satisfactory and when compared with results of unilateral carcinoma of the breast seem to be better, but it must be realized that this is a relatively small group of cases (155) and there was a much larger percentage of patients without axillary nodal metastasis. There was also a higher percentage of lower grades of malignancy. It must also be remembered that many of these patients live many years fol-

TABLE X. BILATERAL CARCINOMA OF THE BREAST IN WOMEN; BILATERAL RADICAL MASTECTOMY AT THE CLINIC FOR NONSIMULTANEOUS LESIONS; A COMPARISON OF RATES IN GROUPS WITH AND WITHOUT AXILLARY METASTASIS

AXILLARY METASTASIS	3 YEARS		5 YEARS		10 YEARS		15 YEARS		20 YEARS	
	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS
Present (48%)	75	64.0	73	43.8	64	32.8	56	25.0	35	14.3
Absent (52%)	80	90.0	74	85.1	58	63.8	36	44.4	27	37.0
Total	155	77.4	147	64.6	122	47.5	92	32.6	62	24.2

lowing the first operation before a carcinoma develops in the remaining breast, the longest interval being twenty-eight years. These survival rates are compiled from the date of the first operation. All of these factors influence the survival rates. It does indicate that even though carcinoma does develop in the remaining breast the results may be very satisfactory.

A study made of patients on whom bilateral radical mastectomy was performed for nonsimultaneous carcinoma of the breast in which either the first or second operation had been done elsewhere is shown in Table XI. This

TABLE XI. BILATERAL CARCINOMA OF THE BREAST IN WOMEN, BILATERAL RADICAL MASTECTOMY (FIRST OR SECOND OPERATION PERFORMED ELSEWHERE, FOR NONSIMULTANEOUS CARCINOMA) A COMPARISON OF RATES IN GROUPS WITH AND WITHOUT AXILLARY METASTASIS

AXILLARY METASTASIS	3 YEARS		5 YEARS		10 YEARS		15 YEARS		20 YEARS	
	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS
Present (55%)	31	48.4	30	30.0	25	8.0	18	0	13	0
Absent (45%)	25	68.0	24	62.5	19	52.6	10	10.0	8	0
Total	56	57.1	54	44.4	44	27.3	28	3.6	21	0

comprises a series of fifty-seven cases. The results shown in this study are not as satisfactory as those shown in Table X. It is impossible to determine definitely the cause for the marked difference of the survival rates in these two series because the extent as well as the grade of the disease of the side done elsewhere is not known but it is probably due to the fact that there was a higher percentage of patients in this group who had axillary nodal metastasis at the time of operation and the lesions may have been more extensive and of higher grade.

Simultaneous.—The results of the study of the three-, five-, ten-, fifteen-, and twenty-year survival rates of bilateral simultaneous carcinoma of the breast are shown in Table XII. This comprises sixty-two patients, or 1 per cent, of the entire series. This study shows that in forty-four, or 71 per cent, of patients nodal metastasis was found in either or both axillae at the time of the radical mastectomy. This percentage is higher than that found in the

TABLE XII. BILATERAL CARCINOMA OF THE BREAST IN WOMEN; BILATERAL RADICAL MASTECTOMY, SIMULTANEOUS OPERATIONS; A COMPARISON OF RATES IN GROUPS WITH AND WITHOUT AXILLARY METASTASIS

AXILLARY METASTASIS	PATIENTS	3 YEARS		5 YEARS		10 YEARS		15 YEARS		20 YEARS	
		PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS	PATIENTS TRACED	PER CENT SURVIVALS
Present (71%)	44	42	28.6	39	17.9	30	3.3	24	0	18	0
Absent (29%)	18	15	66.7	13	61.5	6	50.0	5	40.0	3	0
Total	62	57	38.6	52	28.8	36	11.1	29	6.9	21	0

entire series, which was 60 per cent. No patients who had axillary metastasis survived to the fifteen-year period and only 3.3 per cent who had axillary metastasis survived the ten-year period. There were only eighteen cases in which no axillary nodal metastasis was found at the time of the operation. The results of this series were much more satisfactory than in the group in which metastasis was present but even in this group there was no patient who survived twenty years. These results show the seriousness of bilateral simultaneous malignant lesions, as they are much less satisfactory than the general results of the entire series and much less satisfactory than the results in cases of nonsimultaneous carcinoma of the breast.